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RESPIRATORY VOLUMES OF MEN DURING SHORT EX- POSURES TO CONSTANT LOW OXYGEN TENSIONS ATTAINED BY REBREATHING¹

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Various writers have shown in experiments on men, both with re-breathers and in pneumatic chambers, that an increase in the per minute respiratory volume accompanies rather rapid reduction of the oxygen tension in the air breathed by the subject. Hough ('10, '11) found that the continued rebreathing of a small quantity of air (20 to 30 liters) without the removal of the carbon dioxide produced by the subject, caused a marked increase in the depth of respiration and in the respiratory volume. Twenty-three of his 25 cases showed an increase of respiratory depth from the start of the rebreathing test, and the increase in the depth of respiration was most marked in those cases in which there was some decrease in the rate of respiration. Haldane and Poulton ('08) using a rebreather which removed the carbon dioxide produced by the subject, observed great hyperpnoea when the oxygen in the air breathed was reduced from 10 to 5 per cent in a few minutes. Schneider ('18) reporting on rebreather tests of 25 to 30 minutes duration, states that more than 50 per cent of the men examined gave an increase in respiratory volume when the reduction of oxygen had proceeded to 16 to 14 per cent. Lutz ('19) noted an increase in the respiratory volume of men in the low pressure chamber at a pressure equivalent to 4000 feet altitude, when the pressure was reduced at a rate equivalent to a rise of 1000 feet per minute. Lutz and Schneider ('19)

¹ Abstract, in part, in Proc. American Physiological Society, this Journal, p. 119, vol. xlix, 1919, by authority from S. G. O., dated April 23, 1919.

in a series of experiments both in the low pressure chamber and with the Dreyer nitrogen apparatus found that the onset of increased breathing occurred at about 656 mm. mercury pressure (about 4000 feet altitude) when the reduction in oxygen tension had been made at a rate equivalent to a rise of 1,000 feet per minute. They also state that 9 out of 14 subjects gave a maximum ventilation during the first ten minutes at 20,000 feet, and that following this period there was a distinct falling off in the per minute volume.

The data which follow afford comparisons of the per minute respiratory volumes of 29 men during exposures of 10 to 30 minutes to various constant oxygen tensions lower than the tension of sea level air, with the volumes breathed at sea level and during the reduction of the oxygen tension by rebreathing. Additional data are offered on the increase in respiratory volume during the reduction of oxygen tension by rebreathing. These observations were made as part of the general study of aviation physiology at the Medical Research Laboratory of the Air Service, during the fall and winter of 1918-19. The writer is indebted to Lieutenants H. Fried, C. N. Larsen and B. R. Lutz for assistance during the experimentation.

The rebreather designed by Larsen and Davis (Larsen, '19) was used in these tests. This machine is a portable modification of a closed rebreather in which the carbon dioxide produced by the subject while rebreathing a given volume of air, is removed by a sodium hydroxide cartridge. The rebreather tank contained 54 liters of sea level air at the beginning of each experiment, a volume which the average subject could reduce from 21 per cent oxygen to 9.8 per cent oxygen (equivalent to 20,000 feet altitude) in 20 to 25 minutes. While holding the subject at sea level or at a given oxygen tension, oxygen was supplied automatically to the subject by his own respiratory movements from a balanced oxygen spirometer.

The general plan of each experiment may be summarized as follows. The subject, either sitting or reclining, was connected with the rebreather through a rubber mouthpiece and standard rubber gas-mask tubes. The rebreather spirometer was set at zero and the valves to the subject opened at the end of an inspiration. In this way the spirometer was raised by the volume of one expiration minus the carbon dioxide which was removed as the air passed in through the sodium hydroxide cartridge. One or two inspirations sufficed to lower the rebreather spirometer to zero again, and as the water seal on the oxygen spirometer was broken each time the rebreather spirometer reached the

TABLE I

Average per minute respiratory volume in cubic centimeters; subject sitting

SUBJECT	INITIAL 10 MINUTE PERIOD		REBREATHING PERIOD VOLUMES			AT REDUCED O ₂ LEVEL			TIME OF REDUC-TION
	O ₂	Volume	1-5 minutes	1-10 minutes	10th min-ute to end	Volume	O ₂	Equiva-lent alti-tude	
	<i>per cent</i>						<i>per cent</i>	<i>feet</i>	
AX.....	21.0	6,100	5,840	5,720		5,600	17.4	5,000	9
AE ₁	21.0	9,060	12,240	14,640		13,690	17.4	5,000	11
C.....	21.0	6,140	9,200	10,700		8,120	15.2	8,400	11
D.....	21.0	6,620	9,000	9,460	9,500	7,700	15.4	8,000	10
AF ₁	21.0	7,830	7,800	9,530	10,900	11,100	15.4	8,000	15
AF ₁						10,350 ^a			
B.....	21.0	4,400	5,630	7,880	7,850	7,010	14.8	9,000	14
AB.....	21.0	9,070	10,750	12,590	12,913	12,540	14.3	10,000	17
AB.....						10,006 ^b			
AG.....	21.0	6,550	7,230	8,910	8,440	8,710	14.3	10,000	15
AG.....						6,750 ^b			
AG.....						7,360 ^c			
AA.....	21.0	12,470	16,200	16,440	17,600	16,990	14.3	10,000	12
AA.....		12,720 ^d							
AE ₂	17.4	13,690	16,540			14,800	14.3	10,000	5
AC.....	21.0	6,380	6,300	6,950	6,957	7,250	13.7	11,000	17
AC.....		6,260 ^d							
AD.....	21.0	5,390	5,300	7,090	7,140	6,310	13.7	11,000	15
AD.....		4,890 ^d							
AH ₁	21.0	5,250	5,870	6,960	6,120	5,820	13.7	11,000	15
AQ.....	21.0	6,600	6,700	6,690	7,070	7,760	12.7	13,000	20
AQ.....						7,590 ^b			
R.....	21.0	8,930	9,900	12,070	12,940	13,270	12.3	14,000	20
AJ.....	21.0	7,750	8,900	9,030	9,633	8,340	11.8	15,000	13
AJ.....						8,500 ^b			
AI.....	21.0	10,000	9,800	9,230	10,833	9,910	11.8	15,000	18
AE ₃	14.3	14,800		17,600 ^e		17,500	11.8	15,000	6
AF ₂	15.4	11,100		12,666 ^e		13,600	11.1	16,700	6
AH ₂	13.7	5,820		5,866 ^e		4,180	10.4	18,300	6
AK.....	21.0	6,700	7,460	8,080	8,535	8,420	9.4	21,000	18

^a—average 11th to 14th minutes inclusive.^b—average 11th to 20th minutes inclusive.^c—average 21st to 30th minutes inclusive.^d—average for ten minutes at sea level oxygen tension at the end of the experiment; two minutes elapsed between the last reading at low oxygen tension and the beginning of this ten minute period, during which two minutes the subject was breathing sea level air outside of the rebreather.^e—average 1st to 6th minutes inclusive.

Subnumerals in this table and in tables 2 and 4 refer to successive sections of one experiment.

TABLE 2

Average per minute respiratory volume in cubic centimeters; subject reclining

SUBJECT	INITIAL 10 MINUTE PERIOD		REBREATHING PERIOD VOLUMES			AT REDUCED O ₂ LEVEL			TIME OF REDUCTION
	O ₂	Volume	1-5 minutes	1-10 minutes	10th minute to end	Volume	O ₂	Equivalent altitude	
	per cent						per cent	feet	minutes
I.....	21.0	6,590	7,980	8,330	10,190	12,770	13.7	11,000	18
J.....	21.0	14,050	15,000	15,180	16,100	16,100	13.7	11,000	17
G ₁	21	13,480	12,200	13,560	13,550	14,390	12.6	13,000	12
N ₁	21	11,040	12,000	12,200	12,215	10,960	13.3	12,000	19
Q.....	21	10,780	11,115	11,675		12,600	13.3	12,000	8
N ₂	13.3	10,960	13,300			15,270	12.3	14,000	2
L.....	21	9,050	10,500	11,525	11,492	12,450	12.3	14,000	17
F.....	21	11,320	12,650	13,015	13,030	12,880	12.3	14,000	18
O ₁	21	11,950	12,320	13,860	14,210	12,520	11.8	15,000	20
P.....	21	11,980	11,900	11,820	14,700	12,300	11.1	16,700	15
O ₂	11.8	12,520	12,866			13,305	10.4	18,300	3
G ₂	12.6	14,390	15,633			18,300	10.1	19,000	3
M.....	21	13,010	14,560	18,840		17,370	10.1	19,000	10
H.....	21	11,360	12,000	12,400	13,155	16,540	10.1	19,000	21
K.....	21	8,550	9,200	9,980	10,870				
					10,400 ^a	12,730	9.4	21,000	31

^a—average 21st to 31st minutes inclusive.

zero level, a volume of oxygen equal to that used by the subject during the last inspiration, entered the rebreather tank, before the water seal of the oxygen spirometer again closed. (See Larsen, '19). The subject continued this phase of the experiment using air of sea level oxygen tension until 10 to 15 minutes of normal breathing had been recorded. The oxygen valve was then quietly closed, and without any change in the resistance of the apparatus the subject began the rebreathing of the 54 liters of air in the rebreather tank. The loss of air volume due to the absorption of oxygen by the subject and the correlated absorption of carbon dioxide by the sodium hydroxide cartridge was offset by raising the movable bottom of the rebreather. By means of a scale on the rebreather the per cent of oxygen to which the air in the rebreather had been reduced could be read at any time and the equivalent altitude determined. The composition of the gas in the rebreather was also checked by analyses with a Henderson-Orsat apparatus. When the subject had reached the desired oxygen tension the oxygen valve was again opened and the oxygen tension maintained as at sea level.

The respiratory volume was read each minute from the Larsen respiration integrator (Larsen, '19). The blood pressures and pulse of the subject were taken every other minute as checks on the subject's condition.

The subjects for these experiments, drawn from the Laboratory staff and from the Air Service, were young men in good health, 20 to 30 years of age.

Respiratory volume during the reduction of oxygen tension. Because of the minute to minute variation in the respiratory volume readings, they have been averaged for the first five minutes of oxygen reduction, for the first ten minutes and for the remainder of the reduction period.

From tables 1 and 2 it may be seen that 23 of 29 subjects who began the reduction of oxygen tension at sea level showed an increase in the respiratory volume during the first five minutes of rebreathing, and that 25 of the 29 gave an increase during the first ten minutes. Of the four remaining cases three increased the respiratory volume during the second ten minute period.

By plotting the oxygen reduction as a straight line (the current usage of the Laboratory, verified by analyses made at different stages of rebreather tests—see Air Service Medical, '19) the approximate per cents of oxygen reached by each of the 29 men during the first five and ten minutes of rebreathing were obtained (table 3). These figures show that the increase in respiratory volume appeared very soon after the reduction of oxygen began, as 22 of the 29 subjects had not reduced the oxygen in the rebreather tank air below 18.1 per cent at the end of the fifth minute. The lowest per cent reached by any individual at the end of the fifth minute was 15.6, and the average of all cases was 18.1, equivalent to an altitude of about 4,000 feet. The average per cent reached at the end of the tenth minute was 15.2.

A comparison of the seven cases which began the reduction of oxygen in the air breathed a second time, after remaining at a level of reduced oxygen tension for some minutes, gives an increase in the respiratory volume during the transition period from one level of reduced oxygen tension to a still lower level. Considering all cases, the reduction of oxygen tension was accompanied by an increase in respiratory volume in 32 of 36 cases, regardless of the initial oxygen tension, and this increase in the respiratory volume was initiated in less than ten minutes of rebreathing.

A correlation of the rate of respiration with the respiratory volume in 20 cases indicates that there was little change in the rate of respira-

TABLE 3

Approximate oxygen levels of subjects at the end of the 5th and 10th minutes of rebreathing

SUBJECT	O ₂ AT END OF 5TH MINUTE	O ₂ AT END OF 10TH MINUTE	CHANGE IN RE- SPIRATORY VOLUME DURING FIRST 10 MINUTES	WEIGHT OF SUBJECT
Subject sitting				
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>pounds</i>
AX.....	19.0	17.4	5-	140
AE.....	19.2	17.4	61+	175
C.....	18.2	15.4	74+	168
D.....	19.1	17.3	43+	140
AF.....	19.1	17.3	21+	133
B.....	18.8	16.5	75+	110
AB.....	19.0	17.4	39+	140
AG.....	18.8	16.5	36+	150
AA.....	18.1	15.3	32+	160
AC.....	19.2	17.4	9+	140
AD.....	18.6	16.2	31+	140
AH.....	18.6	16.2	33+	160
AQ.....	18.8	16.6	1+	150
R.....	18.9	16.7	35+	165
AJ.....	17.5	13.9	17+	165
AI.....	18.4	15.9	8-	224
AK.....	17.8	14.6	21+	163
Subject reclining				
I.....	19.0	17.1	26+	144
J.....	18.9	16.7	8+	110
G.....	17.5	13.9	7-	170
O.....	18.7	16.8	11+	160
P.....	17.6	14.3	1-	190
K.....	19.1	17.3	16+	160
N.....	19.0	17.1	11+	160
Q.....	16.1	13.2	8+	130
L.....	18.4	15.9	27+	160
F.....	18.5	16.1	15+	125
M.....	15.6	10.3	43+	133
H.....	18.4	15.9	9+	144

tion during the first ten minutes of rebreathing (table 4). Only 3 of these 20 cases, however, failed to show an increase in the average depth of respiration during the first ten minutes. From this it is evident that the increase in respiratory volume was the result of an increase in the depth of the individual respiration.

Respiratory volume during short exposures to constant low oxygen tension. Table 5 summarizes the comparisons of the respiratory volumes of the subjects while breathing air of a constant oxygen tension lower than the tension of sea level air, after reaching these oxygen

TABLE 4

Average per minute rate of respiration and average depth of respiration in cubic centimeters

SUBJECT	SEA LEVEL		DURING REDUCTION OF O ₂				AT REDUCED O ₂ LEVEL		EQUIVALENT ALTI-TUDE
	Depth	Rate	1st 10 minutes		2d 10 minutes		1st 10 minutes		
			Depth	Rate	Depth	Rate	Depth	Rate	
									<i>feet</i>
AX.....	381	16.0	396	14.4			350	16.0	5,000
AF ₁	524	13.0	768	12.4	908	12.0	925	12.0	8,000
AQ.....	413	16.0	446	15.0	471	15.0	485	16.0	13,000
R.....	539	16.6	726	16.6	779	16.6	799	16.0	14,000
AF ₂			1,005	12.6			1,152	11.8	16,700
AK.....	698	9.6	824	9.8	888	9.6	1,005	8.0	21,000
I.....	366	18.0	438	19.0	509	20.0	751	17.0	11,000
J.....	878	16.0	766	19.8	894	18.0	947	17.0	11,000
G ₁	1,225	11.0	1,013	12.4	1,127	12.0	1,182	12.0	13,000
O ₁	949	12.6	976	14.2	1,000	14.2	963	13.0	15,000
P.....	798	15.0	712	16.6	865	17.0	707	17.4	16,700
O ₂			989	13.0			924	14.4	18,300
G ₂			1,182	13.0			1,800	10.3	19,000
K.....	611	14.0	655	15.0	724	15.0	909	14.0	21,000
K.....					743	14.0a			
N ₁	951	11.6	1,109	11.0	1,018	12.0	800	13.7	12,000
N ₂			1,023	13.0			1,075	14.0	14,000
L.....	1,005	9.0	1,152	10.0	1,149	10.0	1,296	9.6	14,000
F.....	1,617	7.0	1,627	8.0	1,150	8.5	1,842	7.0	14,000
M.....	813	16.0	1,008	17.0			1,022	17.0	19,000
H.....	728	15.6	689	18.0	692	19.0	863	18.0	19,000

a—21st to 31st minutes inclusive.

tensions by rebreathing, with the volumes moved at sea level and during the reduction by rebreathing.

Thirty-two of the 36 subjects breathed a greater volume per minute during the first ten minutes at a constant low oxygen level, than at sea level. These various oxygen tensions were equivalent to altitudes of 5000 to 21,000 feet. The four men who were held at a constant low

oxygen level for 20 minutes and the one man who was held for 30 minutes in low oxygen, each continued to breathe more air per minute throughout their sojourns in low oxygen than at sea level.

The grouping of the cases, if the respiratory volume at the reduced oxygen level is compared with the respiratory volume during the reduction of oxygen by rebreathing, is not so uniform. Seventeen of the 36

TABLE 5

Comparison of the per minute respiratory volumes during the three phases of the experiment

	SUBJECT SITTING	SUBJECT RECLINING	TOTAL
Respiratory volume during first ten minutes at low oxygen level less than respiratory volume during reduction of oxygen but greater than sea level respiratory volume. Group 1.	13	4	17
Respiratory volume during first ten minutes at low oxygen level greater than respiratory volume during reduction of oxygen and at sea level. Group 2.	5a	10b	15
Respiratory volume during first ten minutes at low oxygen level less than the respiratory volume during reduction of oxygen and at sea level; respiratory volume during reduction of oxygen greater than that at sea level. Group 3.	2	1	3
Respiratory volume decreased throughout the experiment	1		
Cases.....	21	15	36

a—Two of these five cases gave a respiratory volume less than the respiratory volume during the reduction of oxygen, during the second ten minutes at low oxygen level.

b—One of these ten cases had exactly the same respiratory volume during the first ten minutes at the low oxygen level and the last ten minutes during the oxygen reduction.

subjects had a lower per minute respiratory volume during the first ten minutes in low oxygen of a constant tension than during the period of rebreathing which preceded this exposure. Of the five men who were held in low oxygen for more than ten minutes four gave a lower respiratory volume for the second ten minutes of the exposure than for the first ten minutes.

The average depth of respiration of the subjects during these exposures to constant low oxygen was greater than at sea level in 15 of 20 cases. The respiratory rate was the same as or lower than the sea level rate in 11 of 20 cases.

DISCUSSION

The increase in respiratory volume during the reduction of the oxygen tension found in these experiments agrees with previous work of other writers who reduced the oxygen tension of the air breathed by their subjects at a fairly rapid rate. The increase here discussed can not be ascribed to the resistance of the apparatus (which was practically negligible) as the subject respired through the apparatus during all phases of the experiment, i.e., during the sea level normals as well as during the reduction by rebreathing and during the exposures at low oxygen levels; nor is it the result of an accumulation of carbon dioxide in the rebreather, as check analyses of the gas in the rebreather were made with the Henderson-Orsat gas apparatus. This increase in respiration does, however, accompany the reduction of oxygen tension and begins very early in the reduction phase of the experiment. Haldane, Meakins and Priestley ('19) offer an explanation of this response by stating that the first result of the diminution of the percentage of oxygen is an increase in the depth of respiration owing to a lowering of the threshold of exciting value of carbon dioxide. This explanation if applied to the present experiments would call for a change in the carbon dioxide threshold very early in the rebreathing reduction of oxygen as the tables show that most of the subjects had responded with an increase in respiration by the end of the fifth minute and to an average oxygen per cent of 18.1. Although the individual minute to minute data for respiratory volume can not be given here, they showed when plotted as curves, a distinct upward trend in every case after the first or second minute of rebreathing, suggesting that the actual increase in respiratory volume began earlier than the fifth minute and at an oxygen per cent higher than 18.1. If the response to reduction of oxygen tension by increase in respiratory volume began above 18.1 oxygen it might have been so small as to be easily masked by other factors and escape notice on the rebreather. That there is a progressive increase in the magnitude of this increase in volume response as the reduction of the oxygen progresses is suggested by a comparison of the per minute volume during the first ten minutes of the rebreathing reduction with the per minute respiratory volume during the second

ten minutes of rebreathing, the volume in the second period being higher in the majority of cases.

Considering the average of 18.1 per cent oxygen as the point at which a definite increase in respiratory volume was found, the responses of 29 subjects examined came earlier in the rebreathing reduction, i.e., at a higher oxygen per cent, than in the cases given by Schneider (l.c.) but at almost exactly the same level as that given by Lutz and Schneider (l.c.) for the onset of increased respiratory volume in their low pressure chamber and Dreyer nitrogen apparatus experiments. It is interesting to note that they found the alveolar carbon dioxide tension definitely lowered at 656 mm. of mercury pressure, which is approximately equivalent to 18.1 per cent oxygen.

The larger respiratory volume moved per minute by subjects during short exposures to low oxygen after a rather rapid reduction in oxygen tension by rebreathing, as compared with their sea level per minute respiratory volumes might be expected in the light of the increase in respiratory volume at 18.1 per cent oxygen. The fall in per minute respiratory volume during the first ten minutes of these exposures to constant low oxygen, to a volume lower than that moved during the reduction of oxygen by rebreathing, in 17 of 36 cases, presents an interesting example of rapid compensation to low oxygen. Lutz and Schneider (l.c.) found a similar fall in the per minute respiratory volume in 9 of 14 cases held at 20,000 feet in the low pressure chamber, and state that they believe this fall in respiratory volume to represent a temporary improvement in the subject's condition. That this fall in respiratory volume does indicate more or less compensation to the new conditions of low oxygen and an improvement in general condition of the subject is suggested in the present experiments by two comparisons.

If the 36 subjects are divided with regard to the per cent of oxygen in the air in which they were held during the exposures to constant low oxygen, i.e., the line of equivalent altitude, 10 of the 36 cases were held at tensions equivalent to altitudes varying from 5000 to 10,000 feet inclusive. Of these ten cases, eight had lower respiratory volumes during the first ten minutes at constant low oxygen levels than during the reduction of oxygen; and the other two cases, although maintaining a higher per minute volume during the first ten minutes at the new oxygen level, decreased their per minute volumes during the second ten minutes of the exposure to constant low oxygen, to volumes lower than those breathed during the reduction of oxygen. These cases held at comparative low altitudes, or comparatively high oxygen per cents,

constitute half the cases in group 1 of table 5. If the per cent of oxygen in the air breathed during these exposures to low oxygen may be taken as a gross index of the severity of the conditions to which the subjects were attempting compensations, the lower the oxygen per cent and the higher the equivalent altitude, the greater the task of adjustment. That the subjects exposed to the less severe conditions did show this fall in respiratory volume during the first ten minutes in constant low oxygen, does therefore favor the view that the fall in respiratory volume (pulse and blood pressure remaining good) is associated with compensations to reduced oxygen tension, which enable the body to maintain itself without so great a per minute respiratory volume.

As shown by the blood pressure and pulse records, subject K was approaching a collapse during his sojourn at 21,000 feet, i.e., he was not maintaining nor improving his condition at that level of low oxygen. His per minute respiratory volume did not fall during the ten minutes he was held at 21,000 feet, but on the contrary continued to increase above the volume breathed during the first, second and third ten minute periods of rebreathing. This case gives the response in respiratory volume of a subject exposed to conditions of low oxygen obviously too severe for his compensatory complex at the time of this particular experiment. The response of subject K also indicates that the fall in respiratory volume of subjects under less severe conditions was correlated with advantageous compensations.

Although the respiratory volume during exposures to constant low oxygen tension was greater than the respiratory volume at sea level, the return to sea level air was accompanied by a very prompt return to the sea level respiratory volume. To check by quantitative methods the general observation made on all subjects, subjects AA, AC and AD were carried through a fourth phase of experimentation. After completing the exposure to low oxygen the valves were opened and the subject allowed to breathe pure, unmixed, sea level air through the rebreather tubes for two minutes. This change to sea level was instantaneous, and it was presumed that the lungs of the subject were fairly well ventilated by breathing outside air for two minutes. At the end of two minutes the rebreather valves were again closed and the subject's per minute respiratory volume while breathing pure sea level air was obtained as at the beginning of the experiment, for an additional ten minutes.

The average per minute respiratory volume of subject AA returned to within 250 cc. of his original sea level respiratory volume, during

this ten minute after-period at sea level, although his increase in respiratory volume at the low oxygen level was 4520 cc. The respiratory volume of subject AC fell during the ten minute after-period at sea level 120 cc., and that of subject AD, 500 cc. below the sea level respiratory volume taken at the beginning of the experiments. The increases in respiratory volumes at the low oxygen levels were 870 cc. and 920 cc. respectively for these two men.

One correlation of the position of the subject during the test with the increase in respiratory volume during the reduction of oxygen by rebreathing seems worthy of note. The per cent of increase in the respiratory volume at the end of the tenth minute of rebreathing was higher for the sitting subjects than for the reclining subjects. As this may be a function of the relative metabolic rate in the two positions, it may be added that Emmes and Riche ('11) found the rate of metabolism in sitting subjects to be 7.6 per cent higher than in reclining subjects, as shown by their oxygen consumption.

SUMMARY

1. The respiratory volumes of 29 men during the reduction of oxygen tension by rebreathing and during short exposures to constant low oxygen tension following the period of rebreathing were studied in connection with the sea level respiratory volumes.

2. An increase in the respiratory volume was noted at the end of the fifth minute of rebreathing, at an average of 18.1 per cent oxygen (approximately equivalent to 4000 feet altitude) in 23 of the 29 subjects.

3. The minute to minute respiratory volumes suggest that this increase may occur even earlier in the rebreathing period.

4. The respiratory volume during the first ten minutes of the exposure to constant low oxygen tension, varying from 5000 to 21,000 feet equivalent altitude, was greater than the sea level volume in 32 of the 36 cases.

5. The respiratory volume of 17 of the 36 cases fell during the first ten minutes of the exposure to constant low oxygen tension to a volume lower than that moved during the reduction of oxygen by rebreathing, although still greater than the sea level respiratory volume. These 17 cases include all but one of the cases held at oxygen levels equivalent to 10,000 feet or less.

6. This fall in respiratory volume during the first ten minutes of exposure to constant low oxygen tension was correlated apparently with compensations to low oxygen advantageous to the subject.

7. The return to sea level oxygen tension was followed by a prompt return to the sea level respiratory volume.

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ALVEOLAR AIR AND RESPIRATORY VOLUME AT LOW OXYGEN TENSIONS

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Modern warfare has not only created a need for quick ascents to high altitudes for brief periods, but has made it necessary frequently for pilots and observers in reconnaissance to remain one or two hours at 15,000 feet or higher. In the light of data recently published (1) from this laboratory, it seems clear that during exposures of an hour or more relatively permanent factors may relieve the more temporary means of compensation which come into play when the ascent is made at the rate of 1000 feet per minute. In connection with the experimental work along these lines there was an opportunity to determine the alveolar air and respiratory volume under conditions which simulated, so far as time and pressure are concerned, an ascent in an airplane to 18,000 or 20,000 feet. Many of the subjects were maintained at these levels for periods varying between 20 and 127 minutes, during which the alveolar air or the respiratory volume was followed.

Few observations have been made under the conditions mentioned above. Haldane and Poulton (2) report great hyperpnoea when the oxygen in the inspired air is reduced from 10 per cent to about 5 per cent in a few minutes. When the reduction was made more slowly, from about 12 per cent to 9 per cent in 30 minutes, there was no noticeable hyperpnoea. The alveolar air fell to values between 3.9 and 4.3 per cent. Schneider (3) reported an increase in lung ventilation, beginning as soon as the oxygen per cent had been reduced by the re-breathing method to 16 or 14 per cent, when the rate of reduction was about equivalent to an ascent of 1000 feet per minute. Lutz (4) has reported that at this rate of ascent the onset of increased breathing may come as early as 656 mm. (4000 feet) in the low pressure chamber.

Many investigators have shown that the lung ventilation is increased at low oxygen levels when the low level is reached after some delay. Loewy (5) reported that the volume of air breathed began to increase

at a reduction pressure of 580 mm. (7000 feet). Loewy and Zuntz (6) found a 4 per cent increase in ventilation when the pressure was reduced to 448 mm. (13,800 feet). Boycott and Haldane (7) found that when the atmospheric pressure was diminished, the alveolar carbon dioxide remained constant until the air pressure fell to 550 mm. (14 per cent oxygen at 760 mm.), or until the alveolar oxygen tension was lowered to about 62 mm. At lower air pressures the carbon dioxide tension fell with increasing rapidity. In these exposures the reduction of the barometric pressure to 350 mm. covered a period of two hours or longer.

Alveolar air tensions found by observers on mountains of moderate height show changes similar to those found in low pressure chamber work. Haldane and Priestley (8) report their alveolar carbon dioxide tensions taken at Oxford and on Ben Nevis (4406 feet). That of J. S. H. fell from 39.6 mm. to 37.0 mm., while that of J. G. P. dropped from 44.5 mm. to 42.4 mm. This change of a little more than 2 mm. was not ascribed to low pressure but to the effects of fatigue, since the subject walked up the mountain. Ward (9) compared his alveolar air values at London, Zermatt (5315 feet) and Monte Rosa (14,965 feet). The entire ascent was made during a period of days, during which his alveolar carbon dioxide tension fell from 37.7 mm. at London, to 34.2 mm. at Zermatt, and then to 28.5 mm. at the summit of Monte Rosa. Such a fall means a marked increase in ventilation. Douglas, Haldane, Henderson and Schneider (10) found a fall of alveolar carbon dioxide from about 40 mm. to 27 mm. The ascent from Manitou (6485 feet) to the summit of Pike's Peak (14,110 feet) was made on the railroad in about an hour and a half. One subject, E. C. S., showed a fall to 33.5 mm. just after arriving; another, Y. H., gave 33.4 mm. Determinations were not made on C. G. D. and J. S. H. until nearly an hour after their arrival. The former gave 32.2 mm., the latter 31.6 mm. FitzGerald (11) determined the alveolar air on persons living permanently at various altitudes up to 14,000 feet and found the carbon dioxide tension already lowered at 700 mm. (2200 feet). Hasselbalch and Lindhard (12), however, report that in steel chamber experiments in which the barometer was lowered from 756 mm. to 541 mm. (10,000 feet) in three or four days, little change in rate or volume of breathing occurred. Mosso (13) did not find any clear-cut increase in ventilation at high altitudes.

It cannot be doubted that there is a lowering of the alveolar oxygen and carbon dioxide tensions at reduced atmospheric pressures. A lowering of the carbon dioxide tension, other things being equal, signifies increased ventilation. However, the changes in the alveolar air and

ventilation which occur when the individual is subjected to conditions comparable, so far as pressure is concerned, to rapid airplane ascents and reconnaissance have not been clearly described.

METHOD

Low oxygen tension was produced by two methods, first by reducing the barometric pressure in a low pressure chamber, and second by the rebreathing method in which the subject gradually reduces the oxygen in a given volume of air, the carbon dioxide being removed by sodium hydroxide. The majority of the experiments reported in this paper were conducted in the low pressure chamber. A number were made with the rebreather for comparison.

The construction of the chamber is described elsewhere (14). While reduction was going on or while a reduced pressure was being held, sufficient ventilation could be maintained to prevent an accumulation of carbon dioxide or oxygen in the respired air. The rate of reduction was uniform and equivalent to an ascent of 1000 feet per minute.

Alveolar air samples were taken in the following manner. After a period of normal breathing ending with an expiration, a quick forced expiration was made into a Henderson alveolar air sampling tube (15). This is essentially a modification of the Haldane-Priestley method of taking an expiratory sample, since the last 75 cc. of the forced expiration remains in the tube. Samples for analysis were drawn directly into a Henderson-Orsat analyzer (16) in which a 1 per cent solution of sulfuric acid in 50 per cent ethyl alcohol was substituted for the 1 per cent acidified water ordinarily used. It was found that such a solution hastened drainage and prevented droplets from standing on the inside of the gas burette, thereby increasing the accuracy as well as the rapidity with which an analysis could be made. Although the method used for taking air samples probably gives slightly higher oxygen and carbon dioxide than more elaborate indirect methods (17), it is pointed out by Pearce (18), (19) that the Haldane-Priestley method is less likely to give such high results for the carbon dioxide than for the oxygen. Certain practical considerations influenced the choice of alveolar air sampling; first, the sample had to be taken quickly while the pressure was being reduced; second, a technique requiring the measurement of air volumes by ordinary spirometers is subject to error in low pressure chamber work when the pressure is being changed. The volume of breathing was determined by two methods. Usually

a continuous record of the volume breathed per minute was obtained. In the first method the subject wore a part of an American Tissot gas mask and inspired through an American light meter no. 5. This meter had a resistance of 3 inches of water to a 20 liter per minute flow. Controls, made at sea level for periods up to 111 minutes, showed no effect

TABLE I

Alveolar air tensions in men during reduction of pressure to 352 mm. (20,000 feet) at a rate equivalent to 1000 feet per minute

	760 MM.		656 MM.		560 MM.		480 MM.		410 MM.		352 MM.	
	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂	CO ₂
1	109.1	40.3	87.1	37.7	68.2	36.4	60.2	31.7	43.6	34.5	39.9	28.0
2	107.0	36.0	93.8	32.5			56.7	33.3	45.7	30.6	27.8	25.9
3	102.8	40.1					50.2	32.6			38.4	26.2
4	105.6	38.5	91.4	33.4	73.8	33.5	58.4	34.5			36.0	31.2
5	109.1	34.9			67.2	36.0	45.4	33.8	40.7	29.2	33.9	27.4
6	99.1	36.2			64.6	32.3	49.3	31.3	40.7	27.9		
7	97.0	41.6	81.6	37.7	69.3	36.2			43.6	27.7	35.1	24.7
8	109.9	36.8							37.4	33.8		
9	102.0	39.5	76.7	38.0	60.0	39.6			38.5	34.8	30.5	30.5
10	87.8	44.8	70.0	39.4	58.5	35.0	47.2	33.3	39.6	30.2	32.9	26.0
11	104.9	41.6	85.2	40.0	63.6	37.4	56.8	34.2	41.4	30.3	36.0	27.6
12	103.4	39.5	92.5	32.5			56.8	31.5	50.1	28.6	36.3	29.3
13	98.5	45.1			62.6	41.2	48.9	38.5	43.2	35.6	34.2	39.8
14	109.9	38.4	86.4	37.1	72.9	35.8	54.1	35.1	42.8	35.6	33.6	33.4
15	104.1	41.3	83.4	38.9	70.8	35.6	57.6	35.9	45.0	34.1	34.8	32.2
16	94.2	40.5	71.8	37.9	58.5	35.1			36.6	32.2		
17	105.6	40.8	86.4	39.4					40.7	32.7	31.7	33.3
18	107.0	37.8			58.5	39.6	50.6	34.8	45.7	30.4		
19	103.4	39.9			68.8	36.4	53.3	33.8			37.5	31.1
20	104.9	37.4			71.4	32.9	57.1	29.0	48.6	28.1	36.6	28.0
21	93.5	44.0	79.7	42.2	66.7	36.8					36.3	32.3
22	107.0	39.6	91.4	33.4	71.8	33.4	52.4	33.2	43.9	27.9	33.9	28.3
23	107.8	38.7					52.4	33.2	41.8	32.4	38.1	30.4
24	104.9	39.5	80.4	35.8	62.1	37.6			41.4	29.2	33.2	35.6
Average	103.2	39.7	83.7	37.0	66.0	36.2	53.3	33.6	42.6	31.3	34.8	30.0

either on the volume per minute or the rate. In the second method a spirometer devised by Larsen (20) was used. In this apparatus the resistance is negligible. It consists of a calibrated spirometer from which the subject inspires through a mouth-piece, a clip being placed on the nose. Each expiration operates an electric valve which opens the spirometer to the low pressure chamber during the expiration and

thus prevents a difference in air pressure inside and outside of the spirometer, which would make the readings valueless.

Alveolar air changes during gradual decrease in barometric pressure. In twenty-four cases in which the subjects were taken to 352 mm. (20,000 feet) at a rate equivalent to 1000 feet per minute, the alveolar tensions were determined for 760 mm., 656 mm., 560 mm., 480 mm., 410 mm. and 352 mm., or sea level, 4000 feet, 8000 feet, 12,000 feet, 16,000 feet and 20,000 feet respectively. The alveolar air tensions are given in table 1. The average figures shown at the bottom of the table are shown graphically in figure 1. The average alveolar oxygen tension at sea level

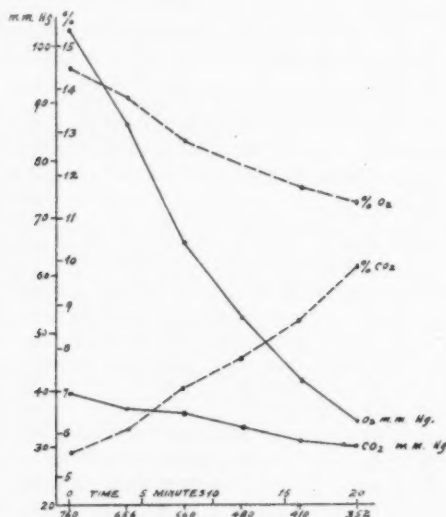


Fig. 1. Average alveolar air changes in 24 men taken to 352 mm. (20,000 feet) in a low pressure chamber at a rate equivalent to 1000 feet a minute.

was 103 mm., and for 352 mm. it was 34.8 mm., thus showing a fall of about 68 mm. or 66 per cent. The maximum fall was from 107 mm. to 27.8 mm., or 79.2 mm. (74 per cent). The minimum change was from 87.8 mm. to 32.9 mm., or 54.9 mm. (63 per cent). The average alveolar carbon dioxide tension for 760 mm. was 39.6 mm., and for 352 mm. it was 30 mm., thus showing a fall of 9.6 mm. or 24 per cent. The maximum fall was from 44.8 mm. to 26.0 mm. or 18.8 mm. (42 per cent). The minimum change was from 39.5 mm. to 35.6 mm., or 3.9 mm. (10 per cent).

These data show a fall in both oxygen and carbon dioxide tensions present at 656 mm. (4000 feet). The fall in carbon dioxide tension was a little more than 2 mm. at this pressure, which corresponds to the drop of a little more than 2 mm. in the alveolar carbon dioxide determinations of Haldane and Priestley (8) taken at Oxford and on Ben Nevis (4406 feet) and which they did not ascribe to low oxygen. The lowered carbon dioxide indicates that an increase in lung ventilation had already begun at this low altitude, although it is difficult to determine this slight increase by measuring the volume of air breathed per minute, as will be seen from data presented later in this paper. This

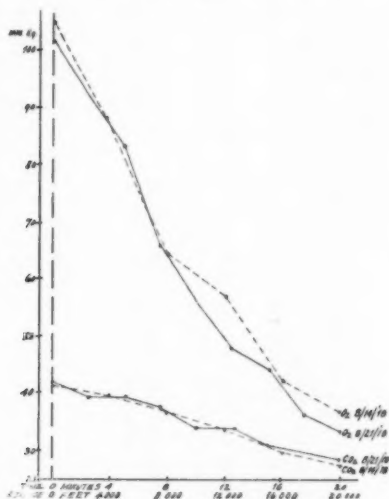


Fig. 2. Alveolar air tensions of J. B. D. taken to 352 mm. (20,000 feet) in a low pressure chamber. Dotted lines on 8/14/18 at a rate of 1000 feet a minute. Solid lines on 8/21/18 at a rate of 500 feet a minute. The carbon dioxide tension of 8/14/18 is plotted 1 mm. lower than the actual value.

early response to low oxygen, which has been quickly produced, is interesting when it is compared with FitzGerald's work (10), which shows a fall in alveolar carbon dioxide present in men living permanently at 700 mm. (2200 feet).

Individual curves show the early fall in alveolar carbon dioxide tension just as strikingly as the average curves. J. B. D. (fig. 2) was taken to 352 mm. on two different days a week apart. On the first

TABLE 2
Alveolar air tensions. Repeated rapid reductions in pressure in the low pressure chamber

TIME MINUTES.....	0	8	15	20	28	35	40	48	55	60	68	75	80	88	95	100	108	115
	760	560	428	428	428	572	700	700	556	428	428	572	700	700	556	428	428	585
Barometer mm. Hg.....																		
E. L. B. 5/14/18 { O ₂ tension.....	102.0	65.7	34.6	34.1	62.6	83.0	88.5	61.0	44.8	43.8	61.9	81.1	88.5	62.0	41.7	39.6	62.5	100.0
CO ₂ tension.....	40.3	35.4	32.6	32.9	37.2	36.5	36.6	35.2	31.0	32.0	35.6	36.1	37.1	34.7	33.8	32.5	35.4	37.4
C. N. 5/14/18 { O ₂ tension.....	104.4	60.7	39.7	41.0	52.0	90.5	87.0	62.0	42.5	36.8	70.0	84.5	73.0	41.3	35.3	65.2	98.4	
CO ₂ tension.....	41.7	39.7	40.3	37.4	44.2	43.5	43.5	42.3	38.2	39.4	39.8	43.5	39.9	37.0	40.5	42.0	41.2	
I. M. 5/13/18 { O ₂ tension.....	106.0	69.5	49.2	52.5	75.5	93.0	99.0		44.4	48.3	70.7	99.5	91.7	70.6	46.9	48.0	65.5	95.0
CO ₂ tension.....	41.0	34.8	31.1	27.3	32.1	34.8	33.2		33.8	29.6	32.2	35.2	37.3	35.3	32.2	28.7	33.5	40.5
TIME MINUTES.....	0	10	15	21	28	35	40	48	55	65	85	93	102					
Barometer mm. Hg.....	760	510	425	430	595	700	700	540	425	425	425	570	760					
A. F. H. 5/21/18 { O ₂ tension.....	106.4	59.8	47.0	43.1	65.2	86.4	91.0	58.5	41.2	38.6	37.5	58.2	93.5					
CO ₂ tension.....	38.9	31.2	30.6	31.7	35.2	35.2	34.8	33.8	31.6	30.1	27.9	34.3	36.7					

day the pressure was reduced at a rate equivalent to 1000 feet per minute, and the reduction was made in 20 minutes. Alveolar air samples were taken every 4 minutes. On the second day the pressure was reduced half as fast and samples were taken every 5 minutes. On the first day the oxygen fell from 105.5 mm. to 37 mm., 68.5 mm. or 65 per cent. The carbon dioxide fell from 42 mm. to 28.2 mm., 13.8 mm. or 32.9 per cent. On the second day the fall in oxygen was 67.5 per cent, and in carbon dioxide it was 32.7 per cent. On both days a definite fall in carbon dioxide tension (2 to 2.5 mm.) was present at 656 mm. (4000 feet).

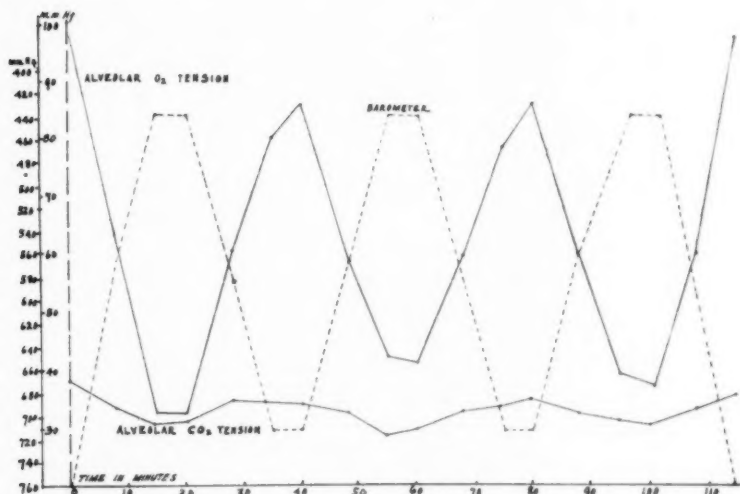


Fig. 3. Alveolar air tensions of E. L. B., 5/14/18, taken three times to 428 mm. (15,000 feet) at a rate of 1000 feet a minute.

That both the alveolar oxygen and carbon dioxide tensions are quickly lowered and quickly returned with rapid reduction, brief exposure, and rapid increase of barometric pressure is shown in four experiments in table 2, the first of which, E. L. B., is seen graphically in figure 3. In these cases the barometer was lowered to 428 mm. (15,000 feet) in 15 minutes, held at that level for 5 minutes, then increased to 700 mm. (2200 feet) at the same rate and held at this new level for 5 minutes, when the ascent was resumed. The reduction of pressure was repeated three times in succession. The fact that the carbon dioxide tension

TABLE 3

NAME	REDBREATH					LOW PRESSURE CHAMBER							
	Date		Alveolar air		Per cent decrease	Final per cent O ₂	Date		Alveolar air		Per cent decrease	Final barometer	O ₂ partial pressure
			760	Final					760	Final			
I. M.....	4/10/18	{ O ₂ CO ₂	100.2 38.8	41.8 32.6	58.1 16.0	9.7	4/17/18	{ O ₂ CO ₂	103.2 40.0	37.1 30.4	64.0 24.0	350	73.5
W. O. K.....	4/22/18	{ O ₂ CO ₂	97.5 43.1	36.1 34.5	63.0 19.9	9.0	4/27/18	{ O CO ₂	104.5 39.5	32.4 30.3	69.0 29.0	325	68.0
H. F. P.....	4/20/18	{ O ₂ CO ₂	102.3 40.4	38.6 32.3	62.1 20.1	9.8	4/30/18	{ O ₂ CO ₂	107.5 38.8	37.9 30.2	64.8 22.2	368	74.5
S. M. J.....	4/30/18	{ O ₂ CO ₂	97.5 45.2	37.0 34.1	62.0 24.8	9.0	5/1/18	{ O ₂ CO ₂	107.0 37.6	33.6 26.7	69.5 29.0	325	68.0
R. M. B.....	4/18/18	{ O ₂ CO ₂	108.0 43.0	37.5 39.4	65.2 8.4	10.3	4/19/18	{ O ₂ CO ₂	105.2 39.7	33.0 34.2	68.6 13.8	365	76.5
E. L. B.....	5/14/18	{ O ₂ CO ₂	105.0 38.3	34.3 35.2	67.4 8.1	10.3	5/15/18	{ O ₂ CO ₂	102.0 40.3	34.6 32.6	66.0 19.1	365	76.5

changed so readily with the pressure indicates that there was little permanent disturbance in the carbon dioxide level, although it should be noted that the carbon dioxide tension did not entirely return to the starting level each time that 700 mm. was reached.

Alveolar air in the rebreathing and in the low pressure chamber methods. In six men the alveolar air tensions in the low pressure chamber and in the rebreathing method were compared. The subjects were first taken on the rebreather. Alveolar air samples were taken by means of a special three-way mouth-piece, about every 4 minutes during the run,

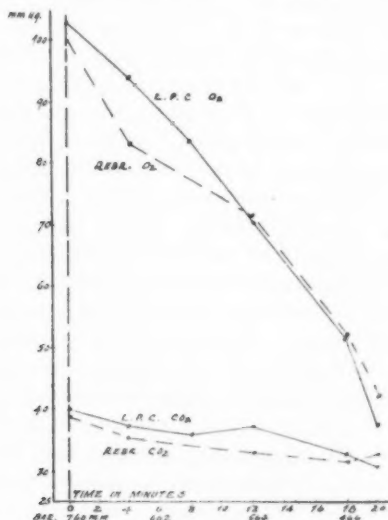


Fig. 4. Alveolar air tensions of R. M. B., 4/18/18, taken on the rebreather to 10.3 per cent oxygen (dotted line). 4/19/18, taken to 365 mm. in the low pressure chamber at the same rate.

with a final sample just as the experiment was stopped. From the percentage of oxygen reached the corresponding barometer was computed and later the subjects were taken in the low pressure chamber to the calculated barometric pressure at a rate corresponding exactly to the reduction of oxygen tension by the rebreathing method. Alveolar air samples were again taken at corresponding times.

The data presented in table 3 and the case of R. M. B. in figure 4 show that the two methods of producing low oxygen partial pressure

are essentially the same so far as the effects on alveolar tension are concerned. In one case the alveolar air tensions were determined in a man taken to 10 per cent oxygen in 20 minutes by the Dreyer nitrogen dilution method (21). In this case the oxygen tension fell from 102.5 mm. to 32.8 mm., and the carbon dioxide pressure from 38.7 mm. to 33.3 mm. Both of these methods emphasize that barometric pressure in itself is not a causative factor in the responses to low oxygen tension except as a means of producing low oxygen tension.

Alveolar air during maintained low oxygen pressure. The alveolar air tensions immediately on ascending to 428 or 380 mm. (15,000 or 18,000 feet) indicate that an increase in ventilation has occurred. There is no doubt that if men stayed long enough at these altitudes they would become mountain-sick. But they may tolerate these altitudes for one or two hours and feel little or no illeffects after the flight. The course of the alveolar tensions during periods of low oxygen level of from 30 to 120 minutes was followed in the low pressure chamber in fourteen cases, by taking alveolar samples every 5 or 10 minutes.

In five subjects taken to 428 mm. (15,000 feet) in 15 minutes and maintained at that pressure for periods varying from 30 to 90 minutes, four showed a fall in carbon dioxide tension during the ascent present at 560 mm. (8000 feet). This fall varied from 1.6 mm. to 4.3 mm. and averaged 3.1 mm. All showed a drop in carbon dioxide tension which averaged 6.7 mm. (7.3 per cent) after having been at 428 mm. for 5 minutes. The average alveolar oxygen tension had fallen from 100.4 mm. to 41.5 mm. at this time, an average drop of 58.9 mm. or 58.6 per cent. In four cases the oxygen tension maintained its low level as the experiment proceeded. In these cases the carbon dioxide tension maintained its new level with little variation. In one case, W. O. K., which lasted 90 minutes, there was a definite rise in oxygen tension during the last 40 minutes, and the carbon dioxide tension fell to 24.4 mm. toward the end. It was evident from these experiments that these men tolerated 428 mm. with little discomfort, since the respiration increased moderately and maintained its new level.

That the men at 428 mm. were not under stress is shown also by the normal alveolar air taken within 20 minutes after 760 mm. had been reached. The carbon dioxide tension of W. O. K. returned only to 34.6 mm. while the others showed a complete recovery to the former tension.

Nine men were taken to 380 mm. (18,000 feet) and maintained at that level for from 50 to 120 minutes. At this altitude more profound changes than those shown at 15,000 feet were expected. The data

TABLE 4
Alveolar air tensions in the low pressure chamber. Subjects taken to 18,000 feet (380 mm.) in 1½ minutes and held at that level

BAROMETER.....		760	540	380	380	380	380	380	380	380	380	380	380	540	760
Minutes.....		0	8-10	18	20-30	380	380	40-50	50-60	60-70	70-80	80-90	90-100		
N. E. F.	6 / 7 / 18	106.6 39.1	65.2 35.8	41.5 30.0	39.4 28.7	37.0 32.0	35.2 33.3	33.6 34.4	34.1 33.2	32.3 33.8	38.1 33.7			50.1 39.0	
R. S. S.	6 / 10 / 18	97.8 38.8			32.7 32.7	33.2 33.5	30.5 33.9	32.1 32.4		32.2 34.2					97.0 39.0
M. G. B.	6 / 11 / 18	107.6 39.5	55.7 39.2	38.9 30.4	35.3 28.6	29.8 32.5	29.7 31.5	30.2 32.4	28.8 31.2	29.0 31.3	34.1 31.5	30.3 32.5			82.6 35.8
H. M. T.	6 / 14 / 18	109.0 38.2	75.5 29.1	38.4 28.6	47.3 21.9	47.7 27.8	43.6 25.6	43.0 23.8	38.2 26.0	44.3 24.2				60.8 27.4	113.0 27.6
B. M. L.	6 / 17 / 18	109.0 37.0		35.8 33.6	32.0 32.9	31.8 33.0	30.8 33.8	31.9 31.1	32.4 30.3					58.1 31.8	107.4 30.5
A. W. L.	6 / 18 / 18	101.3 42.7	54.5 40.5	31.3 34.8	32.0 34.5	30.9 33.7	29.6 34.4	30.3 33.4	30.1 34.3	30.5 33.5	34.3 30.7			66.8 30.4	108.2 35.0
G. C. W.	6 / 25 / 18	98.5 37.1		36.2 29.6	29.7 32.7	30.4 32.3	29.0 31.2	31.8 23.1	31.6 22.4	27.3 26.4				47.6 40.8	97.0 40.6
W. B. M.	6 / 28 / 19	99.5 38.6	63.9 35.1	42.0 32.0	37.6 32.1	32.3 33.6	36.5 34.4	38.2 31.9	32.2 32.8					47.6 37.8	98.0 40.0
B. R. L.	8 / 5 / 18	107.3 37.3	75.0 30.9	44.1 27.4	42.2 29.6	44.0 25.0	50.0 21.0		48.0 22.9	50.4 19.8	43.2 23.4	46.6 21.6		73.0 22.3	113.0 23.8

obtained from this series are presented in table 4. Since alveolar air samples were usually taken every 5 minutes at the desired level, the figures presented represent, for the most part, the average of two samples taken during the period indicated in the table. The average oxygen tension at 760 mm. was 104 mm. It fell to 36.4 mm., 67.6 mm. or 65

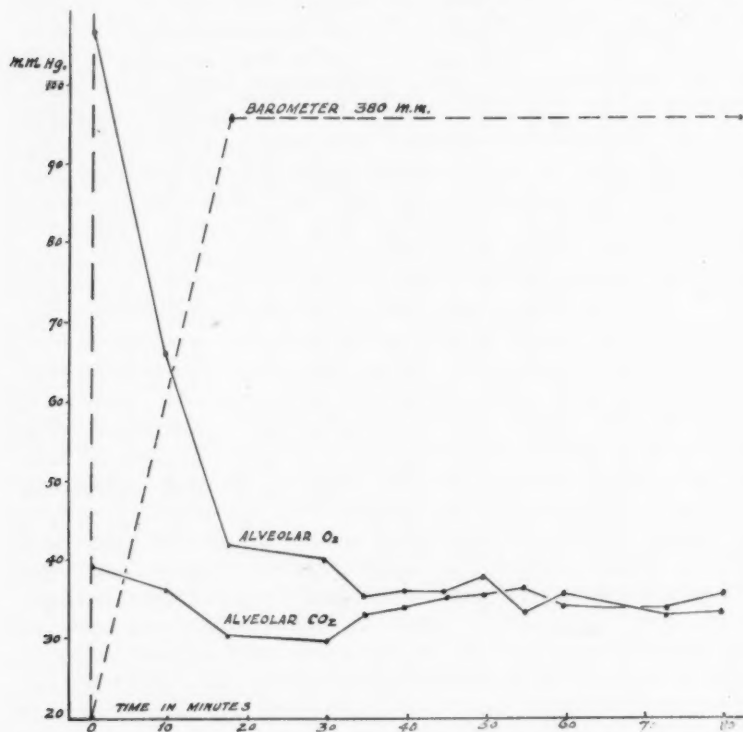


Fig. 5. Alveolar tensions of N. E. F., 6/7/18, taken to 380 mm. (18,000 feet) in 18 minutes and maintained at that level. Note the low carbon dioxide tension just after the low barometric pressure was attained.

per cent, before the subjects had been at 380 mm. for 10 minutes. The average figure had fallen to 34.9 mm. 20 to 30 minutes later. The average carbon dioxide tension at 760 mm. was 38.7 mm. It fell to 30.4 mm., 8.3 mm. or 21.4 per cent, shortly after the subjects had reached

380 mm., but before 10 minutes at that altitude. Twenty to 30 minutes later the average figure had risen to 31. The more profound the effects of 380 mm. over 428 mm. are shown in the percentage of decrease in the alveolar air pressures. For the oxygen it was 58.6 per cent and 65 per cent for 428 mm. and 380 mm. respectively. As might be expected, the more striking effect is shown in the carbon dioxide. The percentage decrease was 17.3 and 21.4 for 428 mm. and 380 mm. respectively.

The alveolar carbon dioxide pressures showed three general types of curves during these experiments. In one case the pressure fell and continued to fall, B. M. L. In two cases it fell and maintained its low level, R. S. S. and A. W. L. In six cases it fell markedly, then rose for a time and either maintained this later level or fell toward the end, N. E. F., figure 5. The majority of cases therefore showed a period of low carbon dioxide tension just after the altitude was reached, followed by a more or less permanent rise. In two of the cases the low point was coincident with the arrival at 380 mm. This is interpreted to mean that the ventilation increases with the ascent and shows its maximum value shortly after the ascent is reached. Following this period there is a tendency toward more quiet breathing. This point will be discussed later in this paper when the data on the volume of breathing are presented.

The after-effects of exposures to a constant low oxygen level are shown in the sea level alveolar airs which were taken just after the subject reached 760 mm. again, that is, about 20 minutes after his exposure to 380 mm. In only four cases did it return to its previous average normal of 38.7 mm., the average normal after the experiment being 34.5 mm. This is shown particularly well in H. M. T. and B. R. L. in table 4. Both of these men responded by deep breathing and maintained an alveolar oxygen tension from 7 to 15 mm. higher than the average. The slow return of the carbon dioxide tension was pointed out by Boycott and Haldane (7), by Schneider (22), and by Douglas, Haldane, Henderson and Schneider (10). Schneider followed the carbon dioxide tension of H. H. R. who had lived on Pike's Peak for about six months. The level did not return to normal for nearly one month and a half and was accompanied by a change in the composition of the blood.

The respiratory volume during reduction of barometric pressure. Alveolar air determinations during the reduction of pressure at a rate equivalent to 1000 feet per minute indicate that an increase in ventilation takes place early and becomes most marked just after the subjects reach 428 or 380 mm. The volume per minute of breathing was there-

TABLE 5
Experiments in the low pressure chamber with the Larsen spirometer. Subjects taken to 18,000 feet (380 mm.) in 18 minutes and held.
Respiratory volume in liters

BAROMETER.....	760				656				560				480					410	395	380	365		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Minute.....																							
E. C. S. 4/29/19	5.82		5.82	8.3	6.66	7.78	9.57	6.27	8.50	8.06	7.17	7.95	7.39	6.27	7.61		8.17	77.50	7.05	7.17	8.28	7.50	
K. O. N. 4/30/19	5.27	4.59	5.04	4.26	5.60	5.49	4.71	5.71	5.71	5.15	6.27	5.83	5.94	5.38	5.60	6.16	6.94	4.82	6.05	6.05	7.06		
N. E. B. 5/6/19	4.98	5.60	5.26	5.04	5.49	4.93	4.71	5.37	5.49	5.15	5.37	5.49	6.05	5.60	5.94	5.94	5.82	5.37	6.72	6.27	5.71	5.82	
B. R. L.* 5/29/19	7.06	7.39	6.16	6.04	7.39	8.28	8.96	7.95	8.96	10.33	9.07	9.40	9.85	9.63	11.20	10.60	12.30	11.90	13.00	13.30	12.70	13.90	
K. O. N.* 5/29/19	7.06	8.95	9.96	8.74	8.95	8.95	9.75	11.00	10.30	10.70	11.50	11.60	11.20	11.50	11.60	11.10	12.20	11.80	11.90	14.60			
E. C. S. 5/29/19	8.40	10.10	10.10	10.30	8.62	7.95	8.40	8.51	7.84	8.28	8.28	8.85	9.51	9.96	10.30	9.07	11.40	11.60	11.60	12.80	11.00	11.90	
G. M.* 5/29/19	9.07	9.07	10.40	8.17	7.50	9.74	8.51	6.84	8.74	8.85	8.74	8.96	8.51	10.50	11.90	9.52	10.10	9.74	12.20	18.40			
B. B. J.* 5/31/19	11.00	10.20	9.86	11.40	11.20	11.30	9.52	10.40	12.00	10.40	9.86	10.70	11.50	11.80	12.50		13.20	12.70					
B. R. L.† 6/2/19	8.74	7.61	7.17	6.27	7.72	5.71	7.72	7.95	9.85	9.07	10.30	8.51	9.74	10.60	11.00	11.90	14.00	13.10	15.70	14.10			
Average.....	7.49	7.94	7.75	7.61	7.68	7.79	7.98	7.78	8.60	8.44	8.51	8.59	8.85	9.07	9.70	9.18	10.50	9.84	10.50	11.60			

* Taken to 19,000 feet in 19 minutes and held.

† Taken to 17,000 feet in 17 minutes and held.

fore investigated. The per-minute volume of breathing was measured with a Larsen spirometer in men reduced to pressures of 395 mm., 380 mm., 365 mm. (17,000, 18,000 and 19,000 feet respectively). The data are shown in table 5. The subjects all showed a considerable increase in breathing varying between 1.8 and 9.3 liters, or 34 and 103 per cent. The average amount breathed per minute at 760 mm. was 7.49 liters. Just as soon as the reduction started the average figure went to 7.94 liters, due no doubt to anxiety of some of the subjects. By the third minute it had fallen to 7.61 liters. The readings thereafter showed a progressive increase until at the 19th minute the average figure was 11.59 liters, an increase of 54.7 per cent. It will be seen both from the average figures and from the individual cases that the onset of increased breathing started usually between the fourth and sixth minutes or between 656 and 605 mm., that is, 4000 and 6000 feet. This confirms the alveolar air findings reported above. The onset of increased breathing due to low oxygen produced by the rebreathing method was reported by Schneider (3) to begin in some cases as early as 16 per cent oxygen, corresponding to about 7000 feet or 580 mm., and by Ellis (23) before 17.5 per cent oxygen was reached. Schneider (3) found in the rebreathing test that the rate remained unchanged for many men but the majority increased the rate by 2 to 4 breaths per minute. The depth of breathing he found increased from 20 to 128 per cent when at 8.5 to 6 per cent oxygen.

The respiratory volume during maintained low barometric pressure. In the majority of alveolar air determinations the lowest carbon dioxide figure was found shortly after the reduced barometric pressure was attained. Thereafter the carbon dioxide level either rose slowly or was maintained. Experiments in which the volume per minute of breathing was measured during a reduction of pressure to 380 mm. at the usual rate and during the following 48 to 84 minutes of the maintained low barometric pressure are tabulated in table 6. Control experiments at 760 mm. using the mask and meter are also shown. The figures given are the three-minute averages in liters. All of the eleven subjects showed an increase in lung ventilation usually most marked within 10 minutes after 380 mm. was reached. Seven showed a reduction of ventilation thereafter continuing until the end of the experiment. Two showed a reduction followed by a terminal rise, which in the case of A. F. H. was very marked. Two cases showed a very slow rise which tended to be maintained until the end. The usual type of response is shown in figure 6, in which the cases of I. M., W. H. G.,

P. S. B. and E. A. R. are plotted. In three subjects taken to 380 mm. at the same rate and held from 59 to 81 minutes the Larsen spirometer was used. Two showed this type of response and in one the increase in respiration continued until the end.

The typical response seen in nine cases out of fourteen in which the volume of breathing was measured, corresponds to that observed in six of the nine cases in which the alveolar air tensions were followed under similar conditions. In one case the subject was taken to 12.5 per cent oxygen in 17 minutes by the rebreathing method and held at

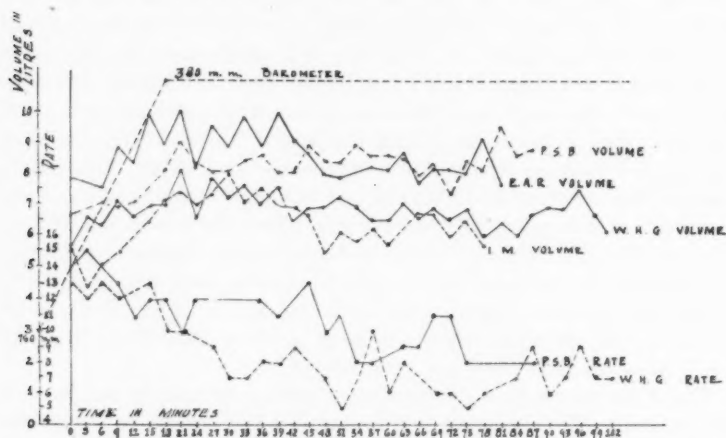


Fig. 6. The respiratory per-minute volume of four cases in liters, taken to 380 mm. (18,000 feet) in 18 minutes and maintained at that level. Note the decrease in ventilation after the maximum is reached. This corresponds to the alveolar CO_2 tensions under similar conditions shown in figure 5.

that level for 68 minutes. The response was similar to the typical low pressure chamber experiment. His per-minute ventilation increased from 8.3 liters to 10.4 liters at the 14th minute. It held a level at about 9.2 liters from that time until the 40th minute, when it gradually fell to 8.4 liters at the 84th minute.

Several subjects taken to 10 per cent oxygen in from 17 to 20 minutes by the Dreyer method showed similar responses. In these cases the ventilation was indicated by a Fitz pneumograph and the average amplitude times the rate per minute was taken as a figure to indicate the per-minute ventilation. I. M. increased from 90 to 252 at the 17th

TABLE 6

Experiments with gas mask and meter. Subject sitting. Respiration in liters per minute. Controls at 760 mm.

MINUTE.....	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90
C. R. S. 6/18/18....		5.85	2.4	6.5	0.5	0.4	2.2	5.3	4.8	4.6	1.8	4.3	4.9	4.1	4.8	4.7	4.2	4.4	4.4	4.5	4.0	4.7									
W. H. G. 7/10/18....		6.37	6.8	2.6	9.5	7.6	9.9	6.3	6.4	6.2	6.7	6.4	7.5	6.4	6.9	5.7	7.7	5.7	0.6	6.6	6.9										
J. J. G. 7/11/18....		9.29	9.9	2.9	2.9	3.9	0.0	8.7	9.0	8.8	8.7	9.0	8.4	9.7	8.4	8.5	9.1	8.7	8.8	8.3	8.7	8.3	8.5	8.4	8.5	8.5	9.8	10.0	8.6	8.9	8.7

Experiments in the low pressure chamber. Subjects taken to 18,000 feet (380 mm.) in 18 minutes and held

I. M. 7/1/18....	5.54	4.45	1.5	4.5	8.6	4.7	1.1	7.4	6.9	7.3	7.9	7.1	7.5	6.9	6.9	6.7	5.4	4.6	6.6	3.6	7.5	5.7	6.3	6.7	6.7	5.9	6.5	5.7			
E. W. B. 6/30/18....	8.19	5.8	7.8	3.8	3.8	6.9	2.1	11.0	8.0	9.3	8.6	9.2	7.9	8.4	9.0	8.1	8.6	7.7	8.9	8.9	8.1	8.6	9.3	8.7	9.0	9.2	8.9	9.6	9.4	7.9	7.7
B. F. 7/2/18....	8.58	2.7	6.7	9.8	1.8	6.8	9.9	9.8	9.4	8.9	9.1	8.9	8.8	8.7	9.2	8.1	7.8	8.8	9.9	4.8	5.8	8.1	8.3	8.2							
D. T. R. 7/3/18....	7.27	7.8	3.7	3.7	8.7	8.9	9.3	7.6	8.1	7.7	8.4	7.4	7.8	7.8	6.9	7.9	7.4	7.3	8.6	9.9	7.4	7.3	7.3	7.6	7.3	8.0	7.1	7.0	7.5	7.2	7.3
H. J. M. 7/5/18....	5.45	7.5	9.4	6.5	9.5	7.5	6.6	6.7	6.0	6.2	6.1	6.4	5.6	6.9	6.3	5.6	5.8	5.5	9.5	0.5	8.6	6.4	6.6	6.6							
A. F. H. 7/8/18....	6.76	8.5	4.4	9.6	2.8	4.9	1.9	9.4	9.0	9.1	10.2	9.2	8.9	9.4	8.3	8.8	2.7	9.7	2.2	7.0	7.5	8.8	7.8	7.3	7.3	7.1	6.3	5.8	4.9	6.0	
P. S. B. 7/9/18....	6.76	8.7	1.6	9.7	2.7	5.8	1.1	9.0	8.3	8.1	8.4	8.6	8.0	8.0	8.9	8.3	8.8	3.8	9.8	8.6	8.6	8.5	7.8	8.3	7.3	8.4	8.2	9.5	8.6	8.7	
W. H. G. 7/10/18....	5.76	6.6	3.7	1.6	6.6	9.7	0.8	16.5	7.8	7.2	7.6	7.0	7.6	6.6	6.8	8.7	2.6	8.6	5.5	6.5	7.0	6.6	6.8	6.6	6.8	6.5	9.9	6.4	6.0	6.7	6.9
A. F. H. 7/15/18....	7.87	6.7	9.7	8.7	4.7	7.8	2.2	9.7	9.3	8.7	9.2	8.9	9.5	9.0	10.2	8.7	6.8	3.8	7.9	0.1	13.8	15.5	16.5	19.8	19.1						
E. A. R. 7/13/18....	7.87	6.7	5.8	8.8	3.9	8.8	4.0	18.2	9.6	8.8	9.9	8.8	10.0	9.1	18.7	7.7	9.7	8.8	8.2	8.1	8.7	7.7	8.2	8.2	8.2	8.0	9.2	7.7			
W. C. W. 7/16/18....	6.66	2.6	1.6	1.6	9.5	9.6	0.7	0.6	5.6	6.6	9.9	6.9	7.6	7.6	7.0	6.7	6.7	6.5	7.4	6.1	6.4	6.7	6.4	6.8	6.2	6.5	6.7	7.1			

minute and then fell to 154 at the 90th minute. This is a picture similar to that of I. M. in table 6 and figure 6. C. L. S. in a similar experiment went from 192 to 360 at the 17th minute and then fell to 128 at the 95th minute.

The rate of breathing was reported in seven cases during the reduction of pressure and the holding period in the low pressure chamber. In four cases it fell from two to five breaths per minute as the experiment proceeded. The rates of W. H. G. and P. S. B. are plotted in figure 6. One showed no change in rate. Two showed an increase, one, N. E. B., from 13 per minute to 15 at 380 mm. and then to 19 at the 82nd minute when the low pressure was maintained. The other, A. F. H., showed no increase until the 58th minute when the rate per minute started to rise from 17 to 38 at the 77th minute. The per-minute volume of breathing increased markedly, as will be seen in table 6.

The tidal air has never been observed to decrease in the low pressure chamber. The majority of subjects responded to the low oxygen exposures by deep slow breathing although frequently Cheyne-Stokes breathing has been observed.

DISCUSSION

The relation of respiration to low oxygen tension presented in this paper is, in a general way, in accord with most of the literature. The early response to decreased oxygen tension and the tendency of the breathing to return toward the normal during maintained low oxygen which we find under the conditions of our experiments, may appear at first sight to be contrary to the views which have been presented by Haldane and others.

Haldane and Smith (24) in 1893 found marked hyperpnoea when the oxygen was reduced to 12 per cent, the carbon dioxide being removed. They write

the fact that any hyperpnoea should have been caused by a reduction of oxygen to 12 per cent may seem at first sight to be hardly consistent with our former conclusions that hyperpnoea caused by vitiated air is entirely due to carbon dioxide.

They explain that in the former carbon dioxide and low oxygen experiments the increased supply of oxygen brought about by the carbon dioxide hyperpnoea prevented an extra hyperpnoea due to want of oxygen from developing. Haldane and Poulton (2) in 1908 reported experiments in which the subjects reduced 25 liters of air from 9

or 10 per cent oxygen to 4 or 5 per cent in less than 10 minutes. They found marked hyperpnoea which they believed was not due to the direct effect of oxygen want but to lowering of the threshold of the respiratory center to carbon dioxide which has not had time to escape. In their experiments, however, the alveolar carbon dioxide fell to between 3.2 and 4 per cent. In another group of experiments the oxygen per cent in the inspired air was reduced to about 9 per cent in from 15 to 23 minutes. In these "no noticeable hyperpnoea" is reported, although the alveolar carbon dioxide fell to between 3.9 and 4.3 per cent, which indicates that a considerable increase in ventilation must have occurred. Haldane, Meakins and Priestley (25) in 1919 conclude, from exposures to low oxygen of about 10 per cent, lasting about 6 minutes, that the first result of diminution in the percentage of oxygen is an increase in the depth of respiration owing to a lowering of the threshold-exciting value of carbon dioxide. This is followed by a period of periodic breathing due to the much quicker action of want of oxygen as compared with that of increase of carbon dioxide. Further reduction of the oxygen percentage showed the periodicity replaced by a very rapid shallow breathing. They write, "Want of oxygen in the inspired air causes shallow breathing which in turn intensifies the anoxemia." The point of view taken by these authors is that after the first period during which the threshold is lowered to carbon dioxide, oxygen want acts as a paralyzing agent on the respiratory center.

We believe that one is not justified in drawing too general conclusions regarding the effects of oxygen want from experiments of extreme degree and short duration. We shall show in a later paper the quick respiratory and circulatory responses to the breathing of pure nitrogen. At the other extreme is the well-known ascent of the Duke of the Abruzzi in the Himalayas to 24,580 feet. In quick extreme anoxemia, respiratory and circulatory factors respond quickly and to their greatest capacity. If the exposure to low oxygen is slow and long-continued, other factors have time to assist in the compensation. We feel, therefore, that the rate of exposure as well as the degree is an important condition when considering the effects of oxygen want. The lack of recognition of this fact brings about confusion. We have never seen a case of shallow breathing and only two cases of increased rate under the conditions of our experiments. They are, however, quite different from those of Haldane, Meakins and Priestley. The decrease in the respiratory per-minute volume, which occurs in our experiments after

the preliminary increase with the reduction of pressure, takes place during exposures of from 30 to 120 minutes rather than during exposures of from 6 to 10 minutes. We do not believe it to be a sign of failing respiratory center, but an indication of improvement in condition, as will be pointed out in another paper.

SUMMARY

1. Twenty-four men were taken to 352 mm. pressure in a low pressure chamber at a rate equivalent to an ascent of 1000 feet per minute. In these cases the average alveolar oxygen tension fell 66 per cent, and the alveolar carbon dioxide fell 24 per cent.

2. The average carbon dioxide tension was definitely lowered at 656 mm. (4000 feet) which indicates that the onset of increased breathing had occurred.

3. Alveolar tensions taken during a reduction of pressure to 380 mm. (18,000 feet) at the usual rate, and during the subsequent 30 to 120 minutes while the low pressure level was maintained, showed that after the preliminary fall in carbon dioxide tension there was a tendency for this tension to rise for a time although it remained low during the holding period. After 760 mm. had been reached again within 20 minutes, the carbon dioxide had not recovered its former level in the majority of cases.

4. The lowest carbon dioxide tension occurred about 5 minutes after 380 mm. was reached, when the reduction was equivalent to an ascent of 1000 feet per minute. In some cases this latent period did not occur and the maximum breathing was coincident with the arrival at 380 mm.

5. Tensions taken while the pressure was maintained at 428 mm. (15,000 feet) did not show the same profound effects. The carbon dioxide tension did not fall so far and maintained a level.

6. Both oxygen and carbon dioxide alveolar tensions responded quickly to rapid successive reductions of barometric pressure to 428 mm.

7. The per-minute volume of breathing was determined for each minute during a reduction of pressure at the usual rate to 395, 380 and 365 mm. The majority of cases showed a definite increase in ventilation taking place between 656 and 605 mm. (4000 and 6000 feet). This final increase amounted to an average of 54.7 per cent. Individual cases varied from 34 to 103 per cent increase.

8. The per-minute volume of breathing was determined during a reduction of pressure to 380 mm. at the usual rate, and during a period

of from 48 to 84 minutes while the low level was maintained. In nine out of fourteen cases the maximum ventilation occurred within 10 minutes after 380 mm. was reached. Following this period there was a distinct falling off in the per-minute volume. These cases correspond to the six cases out of nine in which the alveolar carbon dioxide showed a rise after the preliminary fall.

9. The decrease in the per-minute volume of breathing after the first maximum value, as 380 mm. was reached, was also found in cases in which the low oxygen tension was produced by the rebreathing method and by the Dreyer nitrogen dilution method.

10. The partial return of the respiration toward the normal is believed to indicate a temporary improvement in condition.

11. Alveolar air tensions taken during a reduction of the oxygen partial pressure by the rebreathing method or the nitrogen dilution method corresponded to those taken under reduced barometric pressure.

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COMPENSATORY REACTIONS TO LOW OXYGEN

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In earlier papers we have dealt separately with the blood, circulatory and respiratory changes induced by short periods of exposure to lowered oxygen tensions. It was shown that men responded with definite adaptive physiological changes when subjected to gradually decreasing oxygen partial pressures which reached values between 76 and 51 mm. Hg., corresponding to barometric pressures of from 360 to 240 mm. (19,200 to 29,000 feet), and also when kept for from 30 to 130 minutes at oxygen partial pressures of from 88 to 80 mm., corresponding to barometric pressures of from 425 to 380 mm. (15,000 to 18,000 feet). In approximately 78 per cent of all men examined the erythrocytes and hemoglobin increased in a unit volume of blood. This increase did not occur immediately but usually required between 40 and 60 minutes to become definite. About 13 per cent of all cases showed a well-defined increase in hemoglobin within 26 minutes (1).

The heart responded to slight changes in oxygen tension by an acceleration in the rate of beat. Some men gave the first response at an oxygen partial pressure of 137 mm., barometric pressure 656 mm. (4000 feet); but in the majority the acceleration began between oxygen partial pressures of from 113 to 128 mm., barometric pressures of from 610 to 542 mm. (6000 to 8800 feet). Evidence of an increased rate of blood flow was found in the acceleration of the heart rate, and in a fall in the diastolic blood pressure which resulted in an augmented pulse pressure. When a constant level of oxygen was maintained, the heart reached the maximum rate after a lapse of a period of variable length. It continued at the maximum rate for some time after which the rate retarded somewhat. The evidence indicated that a marked and progressive increase in the rate of blood flow occurred during the reduction and early holding period, after which there followed a period of more or less constant rate of flow. Later in many subjects, as shown by the heart retardation and the rise in the diastolic pressure, the flow of blood in some degree approached the normal rate (2).

The per-minute volume of breathing showed a definite increase between 656 and 605 mm. (4000 and 6000 feet). In the majority of cases the maximum ventilation occurred within 10 minutes after 380 mm. was reached. Following this period there was a distinct falling off in the per-minute volume (3).

In the present paper we propose to consider the relative values of the compensatory reactions to low oxygen tensions. Men differ in sensitiveness to lowered oxygen and in the power to make physiological adaptations which will, from a decreased supply, provide sufficient oxygen to maintain tissue and body efficiency. In some there is an immediate or at least an early response to a decrease in oxygen, in others the response occurs much later and may be less adequate. Some men make excellent compensations to low oxygen tensions while others show insufficient compensations at only moderately low oxygen. Individuals differ also in the use of the several ways of responding to the decrease in oxygen. The majority of men appear to make a well-balanced use of the three mechanisms for supplying oxygen. The ventilation of the lungs, the rate of blood flow and the percentage of red corpuscles and hemoglobin are definitely increased. Some meet the new condition largely by increased respiration and others depend almost entirely upon an increased blood flow. In many individuals, during the early period of exposure to a decreasing oxygen, the burden of compensation is borne wholly by the circulatory and respiratory mechanisms, but later the blood changes relieve one or both of these mechanisms from a part of the burden. Our data show an interdependence and an interplay of the adaptive mechanisms when a subject is held under a constant low oxygen tension. Schneider (4) has reported briefly several cases in which the interplay was present.

The majority of the experiments which have been presented in part in our earlier papers were conducted in the low pressure chamber. The barometric pressure was lowered to 425, 395 or 380 mm. (15,000, 17,000 or 18,000 feet) at the rate of 1000 feet per minute, and held at that pressure for periods varying from 30 to 130 minutes. In a smaller number of experiments the subject breathed atmospheric air diluted with nitrogen by the Dreyer method. Starting with undiluted air, 20.96 per cent oxygen, the nitrogen was added gradually in greater and greater proportion, so that at the end of 20 minutes the mixture contained only 10 per cent oxygen. This percentage of oxygen was then maintained for from 30 to 90 minutes. Thus the subject was kept under low oxygen for a period of from 50 to 112 minutes.

In the low pressure experiments the observers were given oxygen by means of a tube held in the mouth. It was, therefore, necessary to determine whether oxygen accumulated within the chamber during the period of experimentation. In the majority of experiments samples of air were taken 3 to 5 times during the experiment, and later analyzed for oxygen and carbon dioxide. The exhaustion pump was kept working continuously throughout an experiment so that sufficient ventilation was maintained to prevent an accumulation of carbon dioxide. Often there was some accumulation of oxygen, but it was found to reach quickly a constant level. With such data a corresponding correction for altitude was sometimes made. We have, however, many experiments in which no accumulation occurred, and we have usually omitted the correction when the accumulation was slight and the oxygen percentage remained constant during the holding period. We are satisfied that the interpretation of our data is not vitiated by this accumulation. As shown in our earlier papers, the effects upon the blood, circulation and respiration were the same under the three methods used for providing low oxygen tensions. Since this was found to be the case, we have demanded only a constant oxygen tension during the holding period.

THE LOW PRESSURE CHAMBER EXPERIMENTS

The interplay of the three adaptive responses has been studied in forty-seven experiments. For convenience of discussion we have divided the reactions observed during the period at which the barometric pressure remained constant into four groups: *a*, Cases in which the pulse retarded after maintaining a high rate for a period of variable length, and the hemoglobin percentage of the blood increased; *b*, cases in which the pulse maintained the new level after an increase in rate, and the percentage of hemoglobin increased; *c*, cases in which the pulse rate remained constant and the hemoglobin did not increase; *d*, a few cases in which the pulse rate retarded and the hemoglobin did not increase. The variations in respiration have been determined for each of the groups.

a. Retardation of the pulse rate during the holding period with an increase in hemoglobin. There were twenty-six cases in which an increase of hemoglobin seemed to favor the heart and sometimes the respiration. The beneficial cardiac effect, as we interpret the data, was manifested by a slowing of the pulse rate and frequently by a decrease in the blood

flow shown by a rise in the diastolic pressure and a corresponding decrease in the pulse pressure. No two cases were exactly the same. The interdependence of the three compensatory responses can best be shown by a detailed study of a few individual cases.

N. E. F. June 7, 1918. Barometric pressure 380 mm.

	MINUTE								
	0	5	10	15	25	35	55	75	85
Pulse.....	73	75	75	79	82	79	76	72	
Systolic.....	114	112			100	102	104	100	
Diastolic.....	70	72			56	58	58	54	
Pulse pressure.....	44	40			44	44	46	46	
Alveolar O ₂	106		65.2	41.5	37.4	37.0	33.6	32.3	
Alveolar CO ₂	39.1		35.8	30.0	28.7	32.0	34.4	33.8	
Hemoglobin.....	94				96	96		97	100

This subject was in good condition up to the 85th minute when blood was drawn from a vein. It will be observed that during the period of ascent the pulse rate accelerated and the alveolar carbon dioxide tension fell. Thus the burden of compensation to decreasing oxygen was at first borne by the circulation and respiration. The pulse rate reached its maximum four minutes after the barometric pressure of 380 mm. was attained. About this time, the 25th minute, the blood flow as judged from the pulse rate and pulse pressure reached its maximum. Coincident with this the per-minute ventilation of the lungs was greatest as indicated by the carbon dioxide which at this time was only 28.7 mm. The circulatory conditions remained about the same during the next 10 minutes, but the breathing, as judged from the carbon dioxide, was lessened. Both the circulation and the ventilation of the lungs fell off from this time up to about the 60th minute, after which they remained constant to the end of the experiment. It should be noted that the hemoglobin had begun to increase at the 25th minute and continued until the close of the experiment. Coincident with this increase in hemoglobin there was a retardation in the pulse rate and a decrease in the breathing. The interplay of compensatory factors for this case is shown graphically in figure 1.

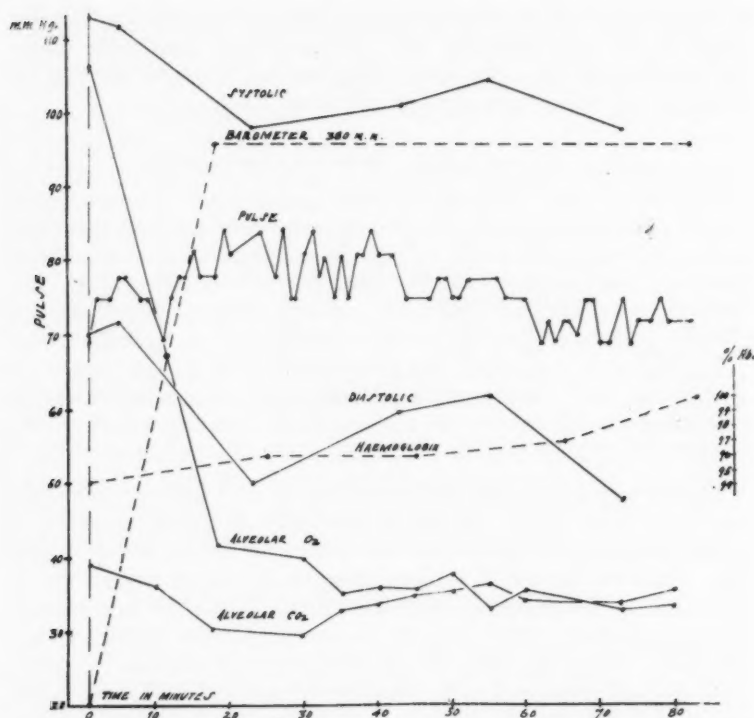


Fig. 1. N. E. F., June 7, 1918. Taken to 380 mm. (18,000 feet) in 18 minutes in the low pressure chamber and maintained at that level. This case illustrates the inter-relation of pulse rate, respiration and oxygen-carrying-capacity of the blood.

R. S. S. June 6, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	45	75
Pulse.....	70	74	76	80	94	90	95	88
Systolic.....	118			114	114	110	106	100
Diastolic.....	70			64	54	48	44	42
Pulse pressure.....	48			50	60	62	62	58
Alveolar O ₂	97.8				32.7	33.2	32.1	32.2
Alveolar CO ₂	38.8				32.7	33.5	32.4	34.2
Hemoglobin.....	102				104	104	106	106

In this subject there was a progressive increase in the rate of blood flow, as shown by the pulse rate and pulse pressure, which reached the maximum at the 45th minute. The pulse rate reached its maximum 10 minutes earlier. We believe that this illustrates that the pulse rate alone did not determine the maximum compensation in circulation. The fall in diastolic pressure with the resulting increase in pulse pressure is considered evidence of vasodilatation in the systemic circulation. Judging by the decrease in pulse rate and in pulse pressure, the rate of blood flow began to slow at about the 58th minute. The respiration attained its maximum soon after a pressure of 380 mm. was reached, and then maintained a fairly constant per-minute volume of ventilation until the end of the experiment. The hemoglobin showed a slight increase at the 25th minute and reached its maximum concentration at about the 50th minute. In this experiment the circulation seems to have been favored by the concentration in hemoglobin while the increase in respiration was maintained throughout.

B. M. L. June 11, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	68	69	70	78	89	91	87	85
Systolic.....	102				102	102	102	102
Diastolic.....	68				52	48	46	46
Pulse pressure.....	34				50	54	56	56
Alveolar O ₂	109			35.8	32.0	31.8	31.9	32.4
Alveolar CO ₂	37			36.6	32.9	33.0	31.1	30.3
Hemoglobin.....	96				96	40th, 99	106	104

In this case the systolic pressure remained constant throughout while in the cases of N. E. F. and R. S. S. it fell. The increase in pulse pressure, as in the case of R. S. S., is again definite and is determined wholly by a fall in the diastolic pressure. The rate of blood flow reached its maximum at about the 35th minute, which was approximately the time of maximum pulse rate. From this time the pulse rate fell gradually about 9 per cent, while the pulse pressure remained high and increased slightly, with the result that the rate of blood flow was presumably reduced. The respiration increased early and then maintained a level until the 50th minute, after which it increased gradually until the end of the experiment. The hemoglobin did not begin to increase until between the 26th and 40th minutes. The pulse rate increased

until the 32nd minute. This suggests a relationship between the hemoglobin and the pulse rate. The increase in breathing is also a factor that may have permitted a slowing of the heart rate.

K. O. N. April 30, 1919. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	84	84	89	94	102	98	95	92
Systolic.....	116				122	120	116	116
Diastolic.....	68				64	58	56	54
Pulse pressure.....	48				58	62	60	62

	MINUTE										
	0	10	15	18	20	32	36	42	49	59	74
Respiration volume..	5.3	5.5	5.7	5.9	6.6	5.7	6.0	5.2	5.4	5.5	5.6
Hemoglobin.....	100		27th, 101		52d, 106		74th, 106				

In this case we determined the per-minute volume of breathing in liters and took the alveolar air occasionally to compare with the volume. The blood flow and respiration each reached the maximum at once on arriving at 380 mm. The pulse rate then held until the 35th minute when it fell slowly until the fall was 12 per cent at the end. The respiratory volume fell slowly until the 42nd minute, after which it held at a volume slightly above the normal ventilation. The hemoglobin was just beginning to concentrate at the 27th minute. It reached its maximum by the 52nd minute. In this case the circulatory and respiratory mechanisms seemed to have been relieved somewhat by the increase in hemoglobin.

In figure 2 the data for P. S. B., July 7, 1918, has been plotted. The pulse rate and diastolic pressure changes indicate that the blood flow reached its maximum during the early part of the holding period, and also that toward the end it decreased markedly. The decrease occurred when the hemoglobin had increased. The respiration was not benefited by the increase in hemoglobin. The remaining twenty-one cases in this group show in a similar manner the relationship between the increase in hemoglobin and the retardation in the pulse rate. We believe that this group of cases represents the usual reaction when the transition from normal oxygen tension to low oxygen is made gradually and at a moderately rapid rate.

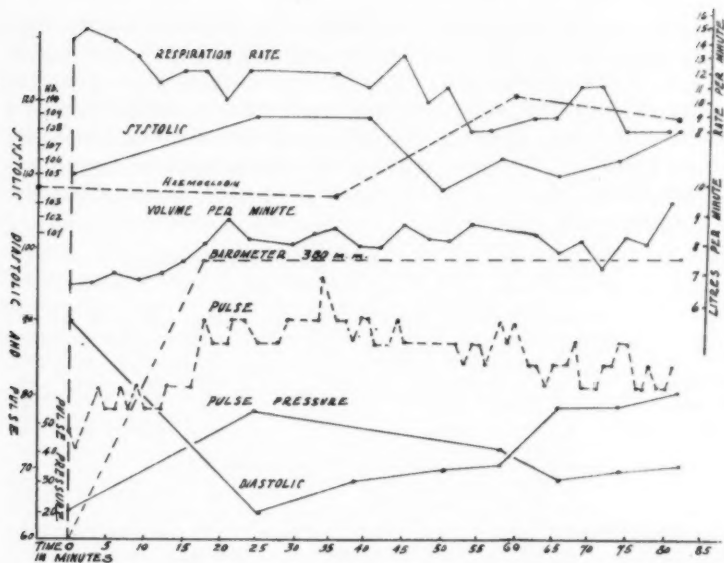


Fig. 2. P. S. B., July 9, 1918. Taken to 380 mm. (18,000 feet) in 18 minutes in the low pressure chamber. This case illustrates the interplay of compensatory factors, particularly the blood flow and the oxygen carrying capacity.

b. Maximum pulse rate maintained with an increase in hemoglobin. There were nine cases in this group, four of which are presented here.

G. C. W. June 25, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	60	62	64	70	78	78	78	82
Systolic.....	100				120	120	118	114
Diastolic.....	60				64	58	48	48
Pulse pressure.....	40				56	62	70	66
Alveolar O ₂	98.5			36.2	29.7	30.4	31.8	
Alveolar CO ₂	37.1			29.6	32.7	32.3	23.1	
Hemoglobin.....	98	82d, 100						

In this case first the pulse, then the systolic pressure, and then the diastolic pressure each in turn aided in maintaining an increased rate of blood flow. The subject appeared to be compensating satisfactorily but his reactions seemed to be insufficient in that the circulatory and respiratory reactions continued to increase even toward the end of the

experiment. The pulse rate was higher after the 70th minute than at any time before. The respiration increased gradually but not so much as in the average case, until the 45th minute, when a marked increase in ventilation took place lowering the carbon dioxide from 31.2 mm. to 22.4 mm. The fact that the respiration increased markedly without affecting the pulse rate shows that the demand for oxygen was not sufficiently cared for. The increase in hemoglobin was slight and not in evidence until the end.

W. C. W. July 16, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	66	69	72	75	88	86	82	90
Systolic.....	104		106	104	102	104	104	102
Diastolic.....	70				52	44	64	60
Pulse pressure.....	34				50	60	40	42

	MINUTE									
	0	5	10	27	30	36	39	54	75	84
Respiration volume.....	6.6	6.2	6.2	6.9	6.9	7.6	7.0	7.4	6.5	7.1
Hemoglobin.....	98	64th, 102			78th, 104					

The heart rate at the 20th minute was 90. It then varied markedly for the next 40 minutes but at the 65th minute it reached 90 once more and showed a tendency to go higher, reaching 95 at times. The respiration reached its maximum per-minute volume at about the 36th minute and maintained it until the 54th minute, after which it decreased slightly. The hemoglobin had increased definitely by the 64th minute. In this experiment, if the hemoglobin exerted any sparing action it was shown in respiration. Compensation seemed to be somewhat inadequate.

E. C. S. April 24, 1919. Barometric pressure 380 mm.

	MINUTE								
	0	5	10	15	25	35	55	75	95
Pulse.....	76	76	80	84	98	100	108	105	102
Systolic.....	108					128	134		126
Diastolic.....	62					62	58		58
Pulse pressure.....	46					66	76		68

	MINUTE								
	0	17	25	33	41	56	81	88	99
Respiration volume.....	5.8	7.4	8.5	8.5	7.4	7.6	7.2	6.6	6.6
Hemoglobin.....	100	29th, 108		57th, 107		77th, 109			

The rate of blood flow undoubtedly increased markedly up to the 35th minute. The pulse rate rose early to a first high point (100), then held on a plateau until the 39th minute, after which it again accelerated until the 46th minute, when it held more or less constant until the end. A slight lowering appeared at the 95th minute. The respiration increased during the ascent and attained its maximum at the 23rd minute. It held this level until the 36th minute, after which the per-minute volume fell and maintained a new level until the 88th minute. During the interval from the 36th to the 42nd minutes, while the respiration was being reduced, the pulse rate rose to its second high point (105). The hemoglobin showed concentration at the 29th minute. In this experiment the respiration seems to have been spared by the increase in hemoglobin. An interplay between circulation and respiration was present during the middle period, from the 36th to the 46th minutes.

N. E. B. May 6, 1919. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	74	74	76	79	86	85	85	84
Systolic.....	108					112	106	104
Diastolic.....	76					70	70	66
Pulse pressure.....	32					42	36	38

	MINUTE						
	0	8	14	18	23	71	82
Respiration volume.....	5.0	5.4	5.9	6.0	6.6	6.7	6.7
Hemoglobin.....	100	42d, 108			76th, 110		

The pulse rate and blood flow reached the maximum together about the 21st minute. The per-minute volume of breathing had increased by the 23rd minute, to the volume which was maintained throughout the holding period. The increase in hemoglobin did not favor either the circulation or respiration.

We believe that some members of this group failed to show an interplay between the hemoglobin, circulation and respiration because they were too near their critical low oxygen limit. The compensations were just able to meet the demand of the tissues for oxygen.

c. Maximum pulse rate maintained without an increase in hemoglobin. There were eight cases in this group. Several of the experiments will

be discussed in the study of repeated cases. It was to be expected that a failure in compensation by one mechanism might cause the others to hold a constant level when they had responded sufficiently to meet the demands of the body for oxygen. The following case is typical of the group.

A. W. L. June 18, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	93	93	96	98	98	100	101	101
Systolic.....	118	120	122	124	120	116	116	118
Diastolic.....	76				78	64	56	60
Pulse pressure.....	42				42	52	60	58

	MINUTE								
	0	10	15	25	45	55	65	75	85
Alveolar O ₂	101.3	54.5	31.3	32.0	29.6	30.3	30.1	30.5	34.0
Alveolar CO ₂	42.7	40.5	34.8	34.5	34.4	33.4	34.4	33.5	30.7

The rate of blood flow appeared to have reached a maximum about the 55th minute and then maintained the new level. The respiration also, after reaching its maximum value at the 25th minute, remained fairly constant until about the 80th minute, when it increased once more. There was no evidence of interplay of compensatory mechanisms throughout this experiment.

d. Retardation in the pulse rate during the holding period with no increase in hemoglobin. There were four cases in this group and the data for these is given below.

F. C. P. December 8, 1918. Barometer 428 mm.

	MINUTE								
	0	5	10	15	25	35	42	50	75
Pulse.....	72	72	74	78	80	77	78	75	74
Alveolar O ₂	97.1		58.1	44.2	44.6		38.6	49.3	38.6
Alveolar CO ₂	39.7		36.7	32.8	30.3		31.9	25.5	31.4

This experiment was conducted at a barometric pressure of 428 mm. (15,000 feet). The breathing as shown by the alveolar carbon dioxide was variable. The carbon dioxide tension was lowest at the 25th and

50th minutes. The high alveolar oxygen tension at the 50th minute was sufficient to account for the falling off in pulse rate.

C. P. C. December 13, 1918. Barometric pressure 428 mm.

	MINUTE							
	0	5	10	15	25	35	45	55
Pulse	84	88	94	98	95	92	88	
Alveolar O ₂	96.0	84.5	56.0	41.6				48.4
Alveolar CO ₂	32.2	22.6	23.3	20.4				18.7

The respiration increased throughout the entire period which probably accounts for the slowing of the pulse rate.

F. D., January 13, 1919, was subjected to a barometric pressure of 395 mm. (17,000 feet) in an experiment which lasted 100 minutes. The hemoglobin did not increase. The pulse rate accelerated from 72 to 99 by the 15th minute. It held this rate for three minutes, was 90 at the 25th minute and 78 at the 70th minute, where it remained until the close of the experiment. The respiration was not measured, but the observer and the subject noticed that the subject's breathing increased and became labored at the 25th minute, and remained so until the end.

H. J. M. June 20, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	65
Pulse	80	83	89	93	100	97	92	100
Systolic	108					112	114	
Diastolic	64					48	48	
Pulse pressure	44					64	66	

	MINUTE							
	0	18	21	24	33	42	57	66
Respiration volume	5.4	5.6	6.7	6.0	6.3	6.3	5.8	6.6
Hemoglobin	No change							

A definite fall in the pulse rate began at the 46th minute and lasted until the 56th minute, after which it gradually accelerated again. There is nothing that accounts for this fall in pulse rate. The arterial pressures were not taken often enough to make an interpretation of the blood flow changes.

We believe that our data accounts, in three out of four of the cases, for the decrease in pulse rate that occurred during the holding period. The interplay in these cases was between the respiratory and circulatory compensations to low oxygen.

REPEATED EXPERIMENTS ON ONE INDIVIDUAL

Five men served as subjects from two to five times each. The data in four cases are complete enough to make comparisons worth while.

W. H. G. May 24, 1918. Barometric pressure 428 mm.

	MINUTE						
	0	5	10	15	25	35	55
Pulse	76	82	85	94	93	91	90
Systolic	100	102	102	102	104	104	100
Diastolic	66			60	62	66	68
Pulse pressure	34			42	42	38	32
	MINUTE						
	0	10	15	25	35	45	65
Alveolar O ₂	106.8	72.5	50.8	45.2	48.8	43.7	46.7
Alveolar CO ₂	37.3	33.0	30.4	31.7	28.9	31.1	28.3
Hemoglobin	96		103	106	106	105	105

W. H. G. July 10, 1918. Barometric pressure 380 mm.

	MINUTE								
	0	5	10	15	25	35	55	75	95
Pulse.....	78	82	90	97	100	98	96	93	94
Systolic.....	110	110	108	114	120	116	116	114	110
Diastolic.....	70				68	68	70	64	64
Pulse pressure.....	40				52	48	46	50	44

	MINUTE									
	0	6	12	21	27	39	42	60	75	102
Respiration volume.....	5.7	6.3	6.6	8.1	7.8	7.6	6.6	6.5	6.8	6.7
Hemoglobin.....	98	46th, 101			65th, 101			95th, 104		

In both experiments the blood flow, as shown by the pulse rate and the pulse pressure, reached its maximum immediately after the low barometric pressure was attained. An increase in hemoglobin was

observed in each experiment when the pulse rate began to retard. The respiration, in the experiment in which the barometric pressure was 428 mm., increased during the ascent, then maintained a level. In the experiment at 380 mm. the respiratory per-minute volume was increased from 5.7 to 8.1 liters during the ascent. It then decreased slowly to 6.6 liters at the 42nd minute, after which it remained constant. In the first experiment the increase in hemoglobin spared the circulation, in the second both circulation and respiration shared the gain.

B. R. L. was taken twice to 380 mm. The results are tabulated below.

B. R. L. August 5, 1918

	MINUTE								
	0	5	10	15	25	35	55	75	95
Pulse.....	84	85	85	88	90	86	84	82	83
Systolic.....	104	102	100	102			92	98	102
Diastolic.....	62			62			60	66	64
Pulse pressure.....	42			40			32	32	38
Alveolar O ₂	107.3		75.0	44.1	42.2	44.0	48.0	50.0	43.2
Alveolar CO ₂ ..	37.3		30.9	27.4	29.6	25.0	22.9	19.8	23.4
Hemoglobin....	107	45th, 111		60th, 112		100th, 112		142d, 116	

B. R. L. May 12, 1919

	MINUTE								
	0	5	10	15	22	25	35	55	66
Pulse.....	85	88	94	94	86	86	88	88	82
Systolic.....	110					110		112	
Diastolic.....	70					70		68	
Pulse pressure.....	40					40		44	

	MINUTE					
	0	5	23	33	46	59
Alveolar O ₂	104.4	90.0	49.3	48.3	51.6	52.0
Alveolar CO ₂	39.1	33.6	31.4	19.5	18.3	18.3
Hemoglobin.....	100	25th, 106		43d, 106	88th, 107	90th, 107

The two experiments, while separated by nine months, were quite similar and unusual in several respects. In both the pulse reached its maximum rate quickly and returned to normal or subnormal before the close of the experiment. The respiratory increase was more marked

than in the usual case, in that the carbon dioxide instead of falling to the average figure of 31 mm., reached 19.8 mm. in the first and 18.3 mm. in the second experiment. A good increase in ventilation occurred during the ascent and it continued to increase for some time after the barometric pressure was maintained at 380 mm. The hemoglobin increased 8.4 per cent in one and 8 per cent in the other. It should be noted that in each experiment the compensation was made at first by the circulation and respiration, but later it was borne wholly by the respiration and hemoglobin, in that the pulse rate slowed to normal or subnormal.

A. F. H. served as a subject four times and did not tolerate the low oxygen tensions equally well each time. The data are summarized in the following protocols.

A. F. H. July 8, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	72	72	75	87	88	87	84	84
Systolic.....	104						94	
Diastolic.....	70						66	

	MINUTE									
	0	15	18	21	24	42	45	54	75	87
Respiration volume	6.7	6.2	8.4	9.1	9.4	9.4	8.3	7.9	7.1	6.0
Hemoglobin.....	99	40th, 100		60th, 104			86th, 104			

A. F. H. July 15, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	69	69	72	72	78	81	79	72
Systolic.....	106	100	98	98	100	104	102	108
Diastolic.....	70				70			72
Pulse pressure.....	36				30			36

	MINUTE										
	0	15	18	21	24	42	45	54	60	66	75
Respiration volume..	7.6	7.7	8.2	9.7	9.3	10.2	7.8	8.7	11.4	15.5	19.1
Hemoglobin.....	94	40th, 95		60th, 95		78th, 98					

A. F. H. July 30, 1918. Barometric pressure 380 mm.

	MINUTE							
	0	5	10	15	25	35	55	65
Pulse.....	78	81	81	86	86	87	90	93
Systolic.....	112		112	108	108	108	96	
Diastolic.....	68		62	70	72	62	58	
Pulse pressure.....	44		50	38	36	46	38	

Respiration not taken.

Hemoglobin: No change.

A. F. H. apparently tolerated a barometric pressure of 380 mm. better on July 8 than during the later exposures. During the first experiment the pulse reached its maximum rate, 90, at the 18th minute. It slowed at about the time the hemoglobin increased. The per-minute volume of breathing showed an early and marked increase which reached its maximum at the 24th minute and held until the 42nd, after which it returned to the pre-experimental volume. The respiration especially and the circulation slightly seemed to have been favored by the increase in hemoglobin toward the latter part of this experiment.

In the second experiment the demand for oxygen was met by an entirely different compensatory reaction. The pulse reached its maximum rate slowly, at the 31st minute, and then remained more or less constant until the 59th minute, when it decreased almost to the pre-experimental rate as the respiration increased. The respiration reached a first high point at the 21st minute, which it held until the 42nd minute. It then decreased for six minutes. At this time a great and progressive increase in breathing began which finally changed the per-minute volume from 7.6 to 19.8 liters. The association of the pulse rate and the respiration was conspicuous in this experiment. The part played by the hemoglobin is obscured by the respiratory response.

In the third experiment, July 30, the respiration was not recorded. The hemoglobin did not increase, and the pulse rate gradually accelerated from 78 to 93 throughout the period of experimentation. This subject had made frequent ascents in the low pressure chamber. He felt more uncomfortable this time than in any previous experiment. He noticed a blurring of vision which had never occurred before.

On May 21, 1918, this subject was taken to a barometric pressure of 425 mm. in 15 minutes, held there for 4 minutes, taken down to 700 mm., held there for about 5 minutes, then taken again to 425 mm. and kept there for 30 minutes. In this experiment the respiratory volume

increased and decreased with the barometer. The pulse accelerated in the first ascent from 74 to 96, then dropped to 70 and accelerated to 82 in the second. The hemoglobin increased from 94 to 98, 4.3 per cent.

These four experiments with A. F. H. show clearly that an individual does not necessarily use the three compensatory mechanisms in equal degree each time he encounters low oxygen tension. It is evident that the burden of compensation may be met adequately in several ways. It appears also that the compensatory changes at a particular pressure may be adequate on some occasions and inadequate at other times. It is probable that A. F. H., if held a little longer at 380 mm., would have developed a typical case of altitude sickness.

W. B. M. served as a subject five times. In the first experiment he was taken to a barometric pressure of 425 mm. and in the others to 380 mm. At 425 mm. the pulse accelerated from 63, reaching its maximum rate, 80, seven minutes after 425 mm. was attained. It held that rate until the 68th minute when it decreased to 76 and remained constant. The hemoglobin gave no evidence of concentration up to the 55th minute, but from the 55th to the 75th minutes it increased from 104 to 110 per cent. The alveolar air showed that the maximum ventilation of the lungs was reached at the 15th minute, after which it took a lower level which was maintained until the end. The compensations were good in this experiment and the interplay of the compensatory factors was evident.

At 380 mm., in the experiments of June 12, 28 and July 31, the pulse after reaching a maximum rate did not fall definitely. The pulse rate in each of the cases showed fluctuations lasting from 5 to 10 minutes. In these the rate retarded at first and then accelerated to the previous high level. The hemoglobin increased during the experiments of June 12 and 28 but did not spare either the respiration or the circulation. In both cases the respiration responded slowly, requiring 42 and 70 minutes to reach the maximum. In the experiment of July 31, the respiration was not studied. The hemoglobin failed to show concentration. The pulse rate and the blood flow reached their maxima shortly after 380 mm. was reached and then maintained that level for 56 minutes, or until the end of the experiment. This subject was again under observation at 380 mm. about five months later, December 27. His pulse at this time accelerated from a rate of 69 at the beginning to 110 at the 28th minute, then quickly retarded to 100 and from this point fell slightly toward the end of the experiment. The pulse showed the same fluctuations in rate as were observed in the earlier experiments

with this subject. The hemoglobin increased 8.8 per cent. We are inclined to believe that a pressure of 380 mm. was too low for this subject. At 428 mm. his compensations were adequate and gave opportunity for an increase in hemoglobin to spare the other factors. At 380 mm. slight movements caused a temporary upset in the balance of the compensatory factors.

The data presented show clearly that on exposure to a decreasing barometric pressure the circulatory and respiratory mechanisms are both stimulated to increased activity. Thus far we have been unable to determine which of these two mechanisms is most sensitive to the change. In many men the heart responded by an acceleration in the rate of beat, and the per-minute volume of breathing increased at about the same time and at barometric pressures that corresponded to relatively low altitudes (4000 feet). Usually the first evidence of response occurred at a higher altitude. Sometimes the pulse rate accelerated before the breathing increased and vice versa. The degree of response made by these two mechanisms is shown to vary with individuals. Thus during the ascent to 380 mm. the pulse rate accelerated from 5 to 30 beats. The volume of breathing also showed corresponding differences.

When a desired pressure was reached and maintained, these mechanisms continued to show differences. The ventilation of the lungs in some men became maximal during the ascent, in others a few minutes after arrival at the constant pressure, while in a few it increased slowly throughout the entire period. The maximum ventilation was likewise maintained for a few minutes, a considerable portion of the time, or for the entire period of the constant pressure. Often after a period of maximal breathing the per-minute ventilation of the lungs was somewhat reduced. In one experiment with A. F. H. it returned to the pre-experimental volume. The pulse rate and blood flow showed a similar variety of changes.

The hemoglobin always increased slowly. In some men no increase could be detected, in others it increased as much as 10 per cent. In a few men the increase began as early as 25 minutes, usually between the 40th and 60th minutes, sometimes as late as the 75th minute. Usually the pulse rate decreased while the hemoglobin increased. Sometimes the pulse rate and the breathing decreased, and in a few instances only the breathing decreased as the hemoglobin concentrated.

The data presented show that the early compensations are made exclusively by the circulatory and respiratory mechanisms. Later

the increase in red corpuscles and hemoglobin shared the burden with the circulatory and respiratory mechanisms. When the early compensation was adequate, as it appears to have been in most cases, the increase in hemoglobin caused a falling off in the activity of either the circulation or the respiration, or both. When the compensation was not adequate, the increase in hemoglobin failed to relieve the other mechanisms to any extent.

That an individual may make equal use of the adaptive mechanisms during several exposures to low barometric pressures is indicated by the repeated experiments on W. H. G., B. R. L. and W. B. M. As illustrated in the four experiments with A. F. H., the responses may differ during two ascents. These experiments show that it is impossible to predict with exactness just how a given individual will react to low oxygen during exposures from 30 to 120 minutes. The three factors of compensation are capable of a variety of combinations. The normal response to low oxygen makes use of the circulatory, respiratory and blood changes.

EXPERIMENTS AT ATMOSPHERIC PRESSURE WITH 10 PER CENT OXYGEN

In this group of experiments the subjects breathed atmospheric air diluted with nitrogen. Starting with undiluted air the nitrogen was added gradually until the proportion gave a mixture that gave 10 per cent oxygen at the end of 20 minutes. This percentage was then maintained. The hemoglobin changes were studied in seven experiments. Three of these gave no increase in hemoglobin and also failed to show a falling off in pulse rate during the period of maintained constant percentage of oxygen. The cases in which an increase in hemoglobin occurred are discussed below.

G. B. H. May 28, 1918. To 10 per cent oxygen in 20 minutes

	MINUTE							
	0	5	10	15	25	35	55	75
Pulse.....	88	90	92	95	103	102	98	102
Systolic.....	110	112	112	110	112	116	110	104
Diastolic.....	70	70	70	66	66	64	62	54
Pulse pressure.....	40	42	42	44	46	52	48	50
Hemoglobin.....	100		70th, 100		82d, 104			

The respiration was recorded by means of a Fitz pneumograph. It showed a definite increase at the 18th minute with a progressive increase to the 38th minute, and then a plateau until the 48th minute. After this a definite falling off in respiration occurred. The pulse rate accelerated until the 20th minute and then maintained a more or less constant level. The blood flow as judged from the pulse pressure reached its maximum about the 35th minute and then held. The increase in hemoglobin came late. The diminution in respiration began before the concentration in hemoglobin was detected. Hence the evidence of an interplay of compensatory factors is uncertain.

W. A. B. gave an excellent response. His data have been plotted in figure 3. The pulse rate reached its maximum about the 20th minute, which was the period of maximum blood flow as indicated by the pulse pressure. The respiration, which was recorded by means of a pneumograph, reached its maximum at about the same time, the 25th minute, and held there until the 38th minute. After this the per-minute volume of breathing decreased somewhat. The hemoglobin had begun to increase at the 22nd minute. In this case the concentration in hemoglobin appears to be definitely related to a diminution in respiration and a decrease in pulse rate.

W. O. K. June 3, 1918. To 10 per cent oxygen in 20 minutes

	MINUTE							
	0	5	10	15	25	35	40	48
Pulse.....	72	75	78	78	78	76	78	86
Systolic.....	110	108	108	112	108	112	112	114
Diastolic.....	78	80	80	78	80	78	70	68
Pulse pressure...	32	28	28	34	28	34	42	56
Hemoglobin.....	100	15th, 102		39th, 106		50th, 108		

The respiration as shown by a pneumograph tracing was somewhat excessive at the start. It quieted later and maintained a constant level until the 48th minute when it suddenly became labored. The depth at this time increased to three times its former value while the rate remained unchanged. There was no evidence of an interplay of the compensatory factors in this experiment. Ten per cent oxygen was too low for this subject, since he fainted at the 51st minute. In a low barometric pressure experiment, at 428 mm., his pulse maintained its maximum rate throughout even though there was a progressive increase in lung ventilation. There was no evidence of an interplay of factors in the experiment.

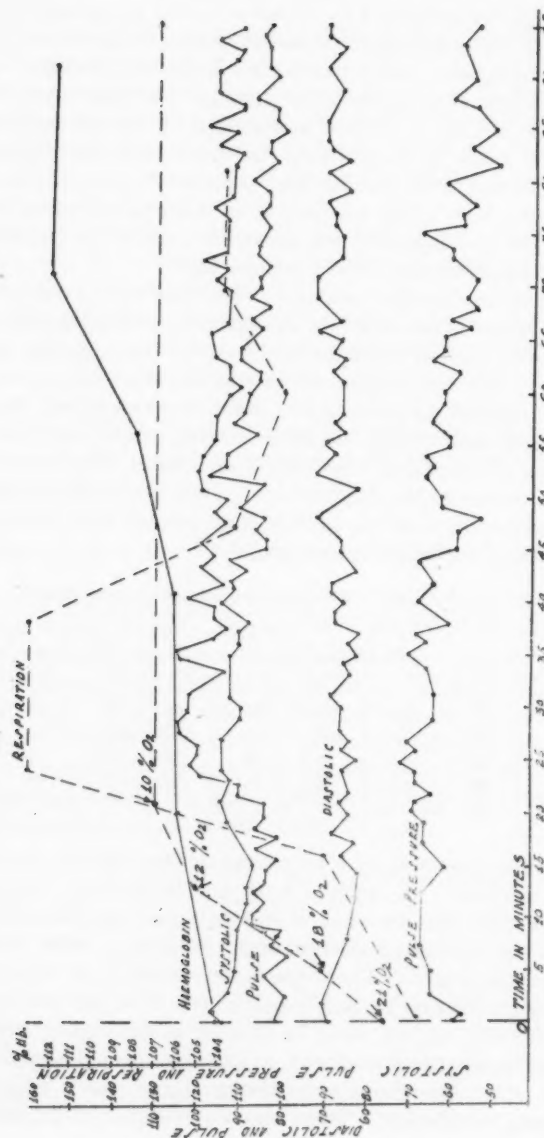


Fig 3. W A. B., May 31, 1918. Taken to 10 per cent oxygen (19,400 feet) in 21 minutes by the nitrogen dilution method. The interplay of blood flow, respiration and hemoglobin is shown. Compare with figures 1 and 2.

E. A. R., in an experiment similar to those just described, gave a 5 per cent increase in hemoglobin which began about the 20th minute. The pulse rate accelerated from 68 to 78 in 32 minutes and then held. The respiration was not recorded. Interplay between the hemoglobin and the circulation was lacking unless it be considered that the early concentration of hemoglobin made it unnecessary for the pulse rate to increase as much as in the other cases. In a low barometric pressure experiment, 380 mm., this subject showed a greater increase in the pulse rate. It accelerated from 72 to 93 and later retarded to 86. His per-minute ventilation increased from 7.8 to 10 liters and then decreased as the hemoglobin concentrated.

We are of the opinion that these experiments were made at too low an oxygen percentage to obtain the optimum response. Ten per cent oxygen, which was maintained during the holding period, is equivalent to an altitude of 19,400 feet. Few men could remain long at such an altitude and escape altitude sickness. Under these circumstances the response made by W. A. B. gives striking confirmation to the view that the effects of low barometric pressure and low percentage of oxygen are due to the same cause, namely, a low partial pressure of oxygen. It also proves that an interplay of the compensatory factors may occur in men subjected to low percentages of oxygen.

We shall not enter here into a discussion of the mechanisms by which the changes observed in these experiments are produced. We desire to point out how the reactions which we have been studying differ from those that occur in men residing at high altitudes. The acclimatization to oxygen want seen in men living at high altitudes involves the same mechanisms that we find in the compensation during a rapid lowering of oxygen tension and comparatively short exposures to low oxygen. Ordinarily on ascending a mountain passively, by railway or automobile, the respiratory response is the first to appear, beginning during the ascent or almost immediately after the summit is reached. It requires, however, several weeks for the respiration to increase to the volume that is normal for the new altitude (5). The blood does not show immediately the increase in hemoglobin and red corpuscles. Just when these changes begin has not been determined, but usually within 24 hours a marked increase in both can be observed. They require five or more weeks to reach their greatest concentration. The pulse also does not ordinarily accelerate immediately but the rate increases slowly during a period of several days. The changes in the breathing and in the blood are permanent in character and do not diminish during

a protracted residence at the high altitude. The changes in the pulse rate and in the rate of blood flow are of a less permanent character. With acclimatization the pulse rate returns somewhat toward the normal rate at sea level. It has been shown also that the longer the period of sojourn at a high altitude the more enduring are the after-effects when the subject again descends to a low altitude. The permanence of these changes has been attributed to diminished alkalinity of the blood, to permanent alteration in the exciting threshold of blood reaction for the kidneys, or to other changes of a more or less permanent character.

The compensations which we have presented in this paper are quick to develop and temporary in character. They disappear at once, or at least quickly, when ordinary atmospheric pressure and oxygen tensions are restored. That they were never quite sufficient at a barometric pressure of 380 mm. was indicated by the fact that while cyanosis often improved when a low oxygen level was maintained, it never disappeared entirely. Furthermore some men who appeared to be compensating well lost gradually in mental efficiency or became abnormally sleepy. It should also be noted that as experience on mountains has demonstrated, if the experiments had been continued several hours longer, the majority of our subjects would have developed typical cases of altitude sickness. Headache and fatigue were often observed as after-effects.

The differences in the responses observed under these two different conditions of exposure to low oxygen depend no doubt upon the suddenness with which the low barometric pressure and low oxygen percentage have been decreased and upon the extent to which they were lowered. In very slow and moderate changes it is possible that no response may be evoked. Possibly the respiratory center, by virtue of greater sensitivity, may react so much to the stimulus that the increase in respiration for a time cares adequately for the oxygen requirement of the body. In the more rapid decrease in oxygen tension the respiratory and cardiac centers and very likely the vasomotor centers are stimulated at higher oxygen tensions and at about the same time. Consequently under the conditions of our experiments these two mechanisms served almost equally to care for the oxygen need of the body.

SUMMARY

1. During a period of gradual reduction in oxygen partial pressure, at a rate approximately 5 mm. per minute, the respiratory and cardiac centers are ordinarily stimulated by about the same fall in the oxygen pressure. In some subjects the first response began at an oxygen partial pressure of 147 mm., in the majority between 128 and 113 mm. In some men the circulation responded before the respiration, and in others the order was reversed. The compensations during the period of reduction, which lasted 15 to 20 minutes, were made entirely by the circulation and respiration.

2. The compensations during an exposure to a constant low oxygen tension were classified as follows: *a*, Those in which the pulse, after maintaining a high rate for a while, retarded slowly and the percentage of hemoglobin increased; *b*, those in which the pulse after a primary rise maintained a constant rate while the hemoglobin increased; *c*, those in which the pulse rate after the primary rise remained constant and in which the hemoglobin did not increase; *d*, those in which the pulse rate after a primary rise retarded and the hemoglobin did not increase. The compensations were distributed among these groups as follows: *a*, 55 per cent; *b*, 19 per cent; *c*, 17 per cent; *d*, 9 per cent.

3. During an exposure of 30 to 145 minutes to low oxygen tension the percentage of hemoglobin usually increased in 20 minutes or more. When this occurred, and when the compensation which had been made by the respiratory and circulatory systems was adequate, the circulation or the respiration, or both, decreased as the hemoglobin increased. In several cases the sparing action of the hemoglobin restored the pulse rate to normal, that is, the pre-experimental rate, and in one case the respiration returned to normal.

4. The interdependence of the three compensatory reactions was shown also in a few cases in which an increase in breathing, following a period of equilibrium in circulation and respiration, resulted in a retardation in pulse rate and blood flow.

5. Several individuals compensated in the same manner and in about equal degree in two or more experiments. One man compensated differently in each of four experiments.

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THE REACTIONS OF THE CARDIAC AND RESPIRATORY CENTERS TO CHANGES IN OXYGEN TENSION

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The fact that the medullary centers of the brain in man are very sensitive to changes in available oxygen became apparent early in the rebreathing and low pressure experiments conducted at the Medical Research Laboratory of the Air Service, Mineola, New York. We (1) have shown that the respiratory and cardiac centers are stimulated to increased activity in some men when the atmospheric oxygen tension is decreased from 159 to 137 mm. Hg. in about four minutes. The respiratory response at first is an increase in the depth but not in the rate of breathing. The cardiac response is shown by an acceleration in the pulse rate. Because these responses developed before the organism appeared to come under stress from lack of oxygen we became interested in attempting to determine how quickly and to what extent the breathing and the rate of heart beat will respond to sudden changes in oxygen tension.

In the past, asphyxia and low oxygen effects have been studied in animals in considerable detail. Paul Bert (2) working with man and animals showed in 1878 that when oxygen was administered at a low barometric pressure in a pneumatic cabinet, the pulse rate retarded soon after the inhalation of oxygen was begun. Traube (3) in 1863 investigated the action of asphyxia upon curarized rabbits. The earlier experiments did not distinguish clearly between the effects due to lack of oxygen and those due to the accumulation of carbon dioxide. The complete separation of the two conditions by the use of such gases as hydrogen, nitrogen or carbon monoxide has proved that the initial effect of oxygen lack on the medullary centers is clearly stimulating (4). Loevenhart has written,

The striking symptoms of asphyxia, however produced, are the following: increase in the rate and depth of the respiration, rise of blood pressure, slowing of the pulse, cessation of respiration, general convulsions followed by paralysis, marked and progressive fall in blood pressure, death.

Gasser and Loevenhart (6) found that decreased oxidation stimulates the medullary centers in the following order: respiratory, vasomotor and cardio-inhibitory, and that on further decrease in oxygen the centers become depressed and finally paralyzed in the order named. Loevenhart has omitted from his list of symptoms of asphyxia the acceleration of the heart which has often been recorded. Lewis and Mathison (7) observe that the heart accelerates within two or three minutes of the onset of asphyxia.

The majority of researches have dealt in detail only with the late and more acute conditions of the reactions to asphyxia and anoxemia. Gasser and Loevenhart (6), however, have determined the latent periods for the action of decreased oxygen on rabbits, dogs and cats by the administration of carbon monoxide and sodium cyanide. The latent periods calculated from the beginning of the administration ranged for the respiratory center between 4 and 14.5 seconds, averaging 6 or 7 seconds, and for the cardio-inhibitory center between 15 and 50 seconds.

In our experiments we have studied men and have confined our attention to the early effects on the heart rate and on the respiration of a reduced oxygen supply. We have also studied the opposite condition in which either oxygen or normal air was given after the individual showed clearly the effects of oxygen want, and we have recorded the heart rate and respiration under these conditions.

METHOD

The effects of anoxemia and the restoration of normal oxygen tension on the pulse rate and respiration were studied by having men breathe pure nitrogen. Nitrogen, saturated with water vapor at room temperature, was supplied through Larsen's spirometer from a rubber bag containing about 80 liters. In a few cases the subjects inspired directly from the bag and exhaled into the room. The Larsen apparatus was used, however, because it gave an opportunity to measure the volume of each breath. Before the experiment the subject sat quietly with a mouth-piece in place but breathing through his nose. Simultaneous records of the pulse and respiration rate and amplitude were taken by means of a Mackenzie polygraph to which a Fitz pneumograph was connected. After sufficient normal record had been secured, with the apparatus still recording, the nose clip was put on and the spirometer opened at the same time so that the subject began to breathe nitrogen without interrupting the record. When the pulse and respi-

ration became markedly increased and the subject began to appear ashy pale, the pupils dilated and unconsciousness impending, the nose clip was removed and the spirometer closed so that the subject breathed atmospheric air without interrupting the pulse and respiratory record, which was continued in most cases until the normal was resumed. No cases of fainting occurred, but it was evident, when the method was being tried out on ourselves, that unconsciousness could come on without fainting, and a few of our subjects were taken to this point.

From the continuous record the pulse was counted for five-second periods throughout. The length of each respiration was measured in seconds and recorded as the rate per minute. The amplitude of each respiration was measured in millimeters. The volume of each breath of nitrogen was read in deciliters from the dial of the respirometer. Unfortunately the return of the per-minute volume, when air was given, could not be followed with the apparatus, but the amplitude of each breath during this period was recorded. In the pulse studies in the low pressure chamber a continuous pulse tracing was taken with the polygraph covering the period before, during and after the taking of oxygen from the tube. In cases in which the effect of oxygen on respiration at low oxygen tension was studied, the Larsen spirometer was used in the low pressure chamber, and at the desired moment oxygen was allowed to fill the spirometer.

The excitability of the medullary centers to changes in the partial pressure of oxygen was determined in two ways; first, by a reduction in available oxygen, and second, by a sudden increase in the oxygen obtained by returning the subject quickly to atmospheric air or by the administration of pure oxygen. By the first method the centers were stimulated and by the second their activity was diminished.

For the determination of the latent period the second method was found to give more uniform results than were obtained by decreasing the oxygen supply. The nitrogen experiments gave the best illustration of this difference. Many of our subjects showed anxiety which was manifested in a high pulse rate and slightly increased breathing. These conditions naturally masked the onset of the stimulating action of the lowered oxygen tension. A further cause for the variation in the length of the latent period was found in the depth of breathing. In passing from the breathing of ordinary atmospheric air to pure nitrogen the depth of breathing was usually so shallow that the amount of nitrogen that passed the dead space of the lungs was comparatively small. It frequently required two or three breaths to alter profoundly the alveolar

oxygen. When the lungs were well filled with nitrogen, the breathing became deep and rapid. Under these circumstances when oxygen was given or the subject was returned to atmospheric air, the first breath because of its depth carried a large amount of oxygen into the alveoli, and since the breathing was also more rapid, a second large influx of oxygen quickly followed the first.

PULSE RATE

The pulse rate data for the nitrogen experiments have been tabulated in table 1. In order that the pulse counts for the entire period might be presented, we have recorded the rate in ten-second intervals. From the polygraph tracings we have taken as our unit five seconds rather than ten seconds. The latent period has been calculated from the beginning of the administration of nitrogen in the study of the effects of decrease in oxygen, and from the time the subject was returned to atmospheric air or given oxygen for the determination of the time of beneficial effects of oxygen. In each case the interpretation consisted of determining in which five seconds the pulse rate had definitely changed in the proper direction, and then of recording the interval that had elapsed up to this five-second period as the length of the latent period. The following are typical experiments with nitrogen in which the pulse rate is recorded in intervals of five seconds.

	BEFORE NITROGEN	NITROGEN ON	NITROGEN OFF	TIME ON
				<i>seconds</i>
J. D.....	6,6,6,7,6,7	7,8,9,9,9,9,9	9,9,7,8,6,6,7,6	42
W. B.....	6,7,6,6,6,6	6,7,8,7,8,9,10,11,10	11,10,9,8,7,8,7,6,6	45
C. L.....	8,8,8,8,9,8	8,8,8,9,9,11,11,11,11	12,11,10,9,8,8,8	46

The latent period for the stimulating effect of a decrease in oxygen during the breathing of nitrogen ranged between 5 and 55 seconds. Approximately 44 per cent of all cases gave a latent period of not more than 10 seconds, and 22 per cent gave one of 15 seconds. Thus a total of approximately 66 per cent of all experiments showed a latent period of 15 seconds or less.

The latent period determined for the opposite action, namely, an increase in oxygen percentage in which the pulse rate was retarded, ranged between 5 and 30 seconds. In about 45 per cent of all cases the latent period was 10 seconds or less, and in 41 per cent between 10

TABLE I

Effects of breathing nitrogen on the pulse rate. Rates calculated from 10 second periods on the sphygmogram. First heavy line indicates time on, second indicates time off

NUM- BER	10	20	30	10	20	30	40	50	60	70	80	90	100	110	120	130	TIME ON
1	72	72	78	72	72	78	78	84	90	102	114	90	90	72	72		71
2	78	72	84	84	84	90	96	96	102	96	96	78					68
3	72	72	72	72	84	84	96	120	126	138	120	96	90	78	84	78	58
4	90	84	96	108	96	108	114	102	114	108	114	114	72				72
5	90	84	90	90	90	102	102	96	102	108	114	114	120	108	96	90	87
6	96	96	102	96	102	120	132	138	126	102	96						47
7	78	84	78	72	78	78	90	90	102	108	108	90	84				64
8	96	96	102	102	102	114	120	126	132	108	102	96					46
9	78	72	72	72	90	102	126	126	114	90	90	72					42
10	102	108	114	114	126	126	132	132	126	114	108	108	102	102	102		39
11	84	84	96	84	96	102	114	114	114	102	96	96	90				57
12	102	108	108	102	114	108	108	108	108	108	108	96	80				80
13	108	114	114	120	132	144	144	150	144	144	126	120	108				40
14	72	78	78	90	108	108	108	108	90	72	78	84					42
15	78	102	96	90	102	108	114	114	114	102	90						48
16	90	90	84	90	84	114	108	108	114	114	108	102	90				60
17	84	78	78	84	84	84	96	102	120	108	90	84					46
18	72	72	72	66	72	66	72	72	78	84	84	90	90	84			88
19	66	72	66	72	72	66	66	78	84	84	96	96	96	84			83
20	90	102	96	96	90	108	114	120	108	104	84						38
21		96	90	96	114	126		132									30
22	102	108	114	120	138	138		126									30
23	90	90	96	102	108	108	102	102	108	114	114	96	96	90	90		66
24	90	96	102	108	114	114	108	108	120	114	102	90	90	84			59
25		90	96	96	96	108	114	114	108		108	102	84	84			63
26	84	84	96	102	114	120	126	120		114	102	90	84	78	84		52
27	102	96	102	108	96	108	108	114	114	102	96	96					47
28	84	90	96	96	102	114	114	120		114	102	96	90	90	90		45

and 15 seconds. A total of 86 per cent showed that the activity of the cardiac medullary center was diminished in 15 seconds or less by an increase of the oxygen in the respired air.

Experiments conducted with ten men in the low pressure chamber in which the subject was held at a barometric pressure of 380 mm. (18,000 feet) gave latent periods similar to those obtained with nitrogen. The oxygen was administered in these cases through a rubber tube held in the mouth. It was customary to give oxygen until the pulse had returned to about the normal rate and then to withdraw the oxygen for five minutes, or until the pulse rate had again accelerated, after

which oxygen was given once more. The following cases in which the pulse rate was recorded for intervals of five seconds are typical.

	BEFORE O ₂	O ₂ GIVEN
B. B. J. { (1).....	8, 8, 8, 8, 8, 8	8, 8, 7, 7, 7, 7, 7, 6, 7, 6, 7
(2).....	8, 8, 8, 9, 8, 9	8, 8, 6, 7, 7, 7, 6, 7, 6, 7, 7
B. R. L. { (1).....	10, 9, 9, 9, 9, 9	9, 9, 8, 7, 8, 7, 8, 7, 7, 8, 7
(2).....	9, 9, 9, 9, 9, 8	9, 9, 8, 8, 7, 7, 8, 7, 7, 7, 7

With one exception the ten men reacted to the oxygen administration by a slowing of the pulse rate which was definite within from 5 to 15 seconds. The exceptional case in two trials gave a latent period of 45 seconds.

The total acceleration of the pulse rate in the nitrogen experiments varied between 6 and 72 beats, although it was usually in the neighborhood of 30. The return to normal, when the subject was restored to atmospheric air, was made in from 10 to 15 seconds. It should be noted that in the nitrogen experiments we did not, as a rule, continue the breathing of nitrogen until the subject became unconscious. In the low pressure chamber the return to normal sometimes required two or three minutes of oxygen administration. In some cases the rate became subnormal.

The above reactions of the heart to changes in oxygen tension bring to mind the discussion of the mechanism by which the observed changes are produced. Gasser and Loevenhart (6) have pointed out that the views on the effect of decreased oxidation on the medullary centers may be classified as follows: *a*, a decrease in oxidation cannot cause stimulation; *b*, decreased oxidation may cause stimulation, but only indirectly by increasing the stimulating effect of carbon dioxide, or by causing the formation and accumulation of acid metabolic products; and *c*, decreased oxygen *per se* under proper conditions will stimulate these centers. They support the third view by proving that the responses of the respiratory and the vasoconstrictor centers occur too rapidly to be attributed to the accumulation of acid products. Our own data on the acceleration and retardation of the heart beat give a reaction time that is also too short to lend support to the acid theory or to the idea of accumulation of metabolic products.

If it be admitted that the variations in oxygen in themselves stimulate and depress the medullary heart center, the question of what

constitutes the accelerator mechanism is still unsettled. It is well recognized that the heart may be accelerated in at least four different ways; *a*, by a decrease in vagal tone; *b*, by stimulation of the accelerator center; *c*, by secretion of adrenin; *d*, by an increase in the temperature of the blood (9). That the low oxygen effect is not the result of a decrease in vagal tone seems likely, since the first action of oxygen want is a stimulating one. Mathison (8) found in animals in which the vagi are intact that irregular slowing occurred frequently during asphyxia. This he attributed to the stimulation of the cardio-inhibitory center. Gasser and Loevenhart (6) also found, in animals under low oxygen produced by the use of carbon monoxide or sodium cyanide, that the latent period for the stimulation of the cardio-inhibitory center varied between 15 and 50 seconds. This period, they find, is often obscured by the rapid onset of the depressive effect of low oxygen on this center. The reaction with which we have dealt in our experiments does not find a ready explanation in decreased vagal tone because the response occurred before the cardio-inhibitory center would have been affected by oxygen want.

Since the first effect of low oxygen on the medullary center is stimulating, it is natural to attribute to the accelerator center the increase observed in exposure to low oxygen of rebreathing and low barometric pressure. Nolf and Plumier (10) believe that in the dog they found evidences of increased tonus in the accelerator cardiac nerves during asphyxia. Mathison (11), on the other hand, demonstrated that the acceleration which immediately preceded heart-block during asphyxia was not due to stimulation of the accelerator center. After sectioning the upper part of the spinal cord to remove the influence of the accelerator center, he still obtained acceleration of the heart. That low oxygen may lead to stimulation of the adrenals has been demonstrated by Kellaway (12). He observed a dilatation of the pupils during such an exposure. We have seen a dilatation of the pupils of some of our subjects during the last part of the period while breathing nitrogen. Meek and Eyster (13) have shown that the action of adrenin is twofold. It accelerates the heart by direct stimulation, and inhibits it reflexly through the vagus, the acceleration occurring first. That an increase in temperature is not the cause of the acceleration follows from the briefness of the nitrogen experiments in which the acceleration was evident within 5 to 15 seconds.

We believe that the acceleration which we have reported in this paper and in our study of low pressures and low oxygen percentages,

occurs before the cardio-inhibitory effects observed by Gasser and Loevenhart and by Mathison. It is not the same acceleration that Gasser and Loevenhart found after the depression of the inhibitory center. That it is a result of a stimulating action on the accelerator heart center seems to us the most satisfactory explanation. We have, however, no experimental proof for this explanation.

The beneficial or quieting effect of oxygen on the heart rate has been observed by Benedict and Higgins (14) and by Parkinson (15). In normal individuals at sea level the breathing of oxygen-rich mixtures slowed the rate appreciably. Schneider and Sisco (16), working on Pike's Peak (14,110 feet), administered oxygen to six subjects and observed a reduction in the pulse rate which varied between 7.4 and 28.8 per cent, while in Colorado Springs (6000 feet) the breathing of pure oxygen caused a slowing of from 2.5 to 8.8 per cent.

RESPIRATION

The response of the respiratory mechanism to changes in oxygen tension was studied by the same methods and at the same time as the pulse rate changes were under observation. The respiration was recorded by means of a pneumograph and a Mackenzie polygraph. In some cases we have also measured the volume of breathing by means of the Larsen spirometer. From the polygraph tracing the height of the curve of each respiration has been measured to determine a factor which would give relative data on the change in volume of each respiration. The rate of breathing has been determined by noting the time taken for each breath.

A summary of the results obtained with nitrogen is given in table 2. In table 3 the results of six experiments are presented in detail. In the nitrogen experiments we dealt with opposite conditions, a reduction in oxygen tension and an increase in oxygen tension. In the presentation of the pulse rate changes it was shown why the latent period as determined for the effects of decrease in oxygen would be longer than that for the effects of increase in oxygen. In addition to the influence of the depth of breathing, the rate of blood flow may account for the shorter latent period that occurred when the subject was returned to normal atmospheric air. During the early stages of asphyxia, Mathison (11) found in animals that the systolic output per beat gradually increased, reaching a maximum in about 30 seconds. Since the effects of the oxygen changes are brought about through the action on the

TABLE 2

Effects of breathing nitrogen on respiration. The latent periods for the initial response in both rate and depth, when nitrogen is on and off, are given

NUMBER	RATE					HEIGHT					VOLUME		
	On; latent period	Normal per min-ute	Maximum per min-ute	Off; latent period		On; latent period	Normal	Maximum	Off; latent period		On; latent period	Deciliters per breadth	
				Begin	Complete				Begin	Complete		Begin	Maximum
sec.			sec.	sec.	sec.	mm.	mm.	sec.	sec.	sec.			
1	32	13	27	19		19	5	26	10		14	2.50	19.10
2	60	14	23			8	4	20	9	18	17	2.80	15.70
3	50	16	23			4	4	9	4		4	5.60	14.80
4	26	16	27	7		7	4	22	5		7	6.70	26.30
5	8	17	26	5		4	5	21	3	45	4	3.90	8.95
6	55	16	29	7	20	22	4	16	10	31	18	6.20	17.40
7	20	18	24	12	12	20	6	14	3		23	2.24	5.60
8	45	17	30	11	25	13	5	22	6	27	13	2.80	8.96
9	33	15	17	4	17	21	14	25	9	14	6	8.40	19.60
10	20	14	29	31	31	22	4	8	24	31	6	3.90	7.84
11	27	12	17			35	5	10			23	8.40	13.40
12	31	18	30	6	11	15	4	13	3	11	15	4.50	10.80
13	26	20	50			18	4	17	15	25	15	2.80	7.80
14	32	15	25	11	32	12	3	25	5	21	4	1.12	12.20
15	41	18	21			9	4	28	5	10	9	6.72	19.10
16	48	18	27			7	4	30			7	2.24	22.40
17	61	15	23	4	13	25	3	17	8	23	25	2.24	7.84
18	80	26	38			17	3	10	7	17			
19	48	8	15			28	9	16	10				
20	48	9	11		25	12	6	12					
21	25	13	37	9		20	12	30	9				
22	10	18	25	2	10	10	7	25	2	15			
23	21	13	23	7		12	6	13	3				
24	25	14	35	3		12	4	15	3	20			
25	34	15	20	15		12	8	27	11	35			
26	22	17	20			22	5	17	5	21			
27	47	18	25	3		10	5	16	6	21			
28	25	21	30	8	22	10	9	22	3	26			
29	18	23	46	19	37	5	7	20	5	48			
30	48	10	27	7	14	13	6	20	6	53			

J. E. J.					E. C. S.					S. I.				
Number of respirations	Length	Rate per minute	Height	Volume	Number of respirations	Length	Rate per minute	Height	Volume	Number of respirations	Length	Rate per minute	Height	Volume
	sec.		mm.	decil.		sec.		mm.	decil.		sec.		mm.	decil.
0	3.5	17	4		0	4.3	14	3		0	2.5	24	5	
Nitrogen on					Nitrogen on					Nitrogen on				
1	4.0	15	3	1.12	1	3.8	16	4	2.80	1	4.0	15	4	3.36
2	4.0	15	3	2.24	2	4.2	14	4	3.90	2	3.3	18	5	2.80
3	4.0	15	4	3.36	3	4.6	13	6	5.60	3	2.6	23	5	1.68
4	4.0	15	3	5.60	4	4.5	13	5	2.80	4	3.1	19	5	5.04
5	4.2	14	6	5.60	5	7.5	8	7	5.04	5	2.8	21	5	3.90
6	4.2	14	9	6.72	6	4.2	14	9	6.16	6	3.0	20	6	3.90
7	4.0	15	9	6.72	7	4.8	12	9	7.84	7	3.0	20	7	5.04
8	4.2	14	10	6.72	8	4.6	13	11	7.84	8	3.0	20	6	5.60
9	3.8	16	12	7.84	9	4.3	14	9	8.40	9	2.8	21	6	4.48
10	3.8	16	13	8.96	10	4.4	14	11	7.84	10	2.7	22	6	3.36
11	3.6	17	13	7.84	11	4.4	14	12	8.40	11	2.7	22	6	6.16
12	3.8	16	16	11.20	12	4.3	14	14	12.89	12	4.2	14	7	5.01
13	3.6	17	17	10.10	13	4.3	14	14	11.20	13	2.5	24	8	4.12
14	3.2	19	18	10.10	14	3.8	16	15	15.68	14	2.5	24	9	5.60
15	3.4	18	18	11.20	15	3.6	17	20	14.57	15	2.2	27	10	6.16
16	3.0	20	19							16	2.2	27	11	5.04
17	2.6	23	20	11.20	Nitrogen off					17	2.2	27	11	6.72
18	2.8	21	21	10.10	16	3.5	17	15		18	2.5	24	11	5.60
19	2.4	25	24	12.20	17	2.9	21	17		19	2.2	27	12	6.72
Nitrogen off					18	3.0	20	15		20	2.2	27	13	6.72
20	2.4	25	23		19	3.0	20	13		21	2.2	27	13	7.84
21	2.4	25	25		20	2.9	21	9		22	2.1	28	15	6.72
22	2.4	25	19		21	3.0	20	7		Nitrogen off				
23	2.4	25	12		22	2.7	22	4		23	2.2	27	17	
24	2.4	25	17		23	2.4	25	4		24	2.2	27	14	
25	3.4	18	13		24	3.0	20	3		25	2.2	27	15	
26	3.4	18	10							26	2.4	25	15	
27	3.43	18	8							27	2.8	21	15	
28	4.0	15	5							28	2.8	21	12	
29	3.6	17	5							29	2.2	27	15	
30	3.8	16	5							30	2.2	27	11	
31	4.0	15	5							31	1.8	38	5	
32	4.0	15	5											

TABLE 3—Concluded

W. B.					C. H. L.					K. O. N.				
Number of respirations	Length	Rate per minute	Height	Volume	Number of respirations	Length	Rate per minute	Height	Volume	Number of respirations	Length	Rate per minute	Height	Volume
0	4.3	14	3	decil.	0	2.6	23	5	decil.	0	3.7	16	4	decil.
Nitrogen on					Nitrogen on					Nitrogen on				
1	3.2	39	4		1	3.2	19	4	4.48	1	3.6	17	6	6.72
2	2.7	22	5	3.90	2	2.7	22	4	6.16	2	3.6	17	7	6.16
3	3.7	16	4	6.16	3	3.3	18	4	3.90	3	3.2	19	10	8.40
4	4.2	14	5	4.48	4	3.3	18	4	4.48	4	2.9	21	14	9.52
5	3.0	20	5	4.48	5	3.6	17	6	5.60	5	2.9	21	15	14.00
6	2.5	24	5	5.60	6	3.3	18	7	8.40	6	3.2	19	19	14.60
7	2.8	21	7	4.48	7	3.2	19	7	7.27	7	3.9	15	20	26.30
8	2.8	21	7	6.16	8	3.2	19	10	7.84	8	3.5	17	19	22.40
9	2.8	21	7	6.72	9	3.2	19	10	11.20	9	3.2	19	19	16.80
10	2.5	24	7	6.72	10	2.3	26	7	10.80	10	2.9	21	20	24.60
11	2.6	23	7	7.27	11	2.6	23	7	5.60	11	2.2	27	20	19.10
12	2.5	24	7	6.72	12	2.7	22	9	10.80	12	2.2	27	20	
13	2.4	25	9	7.84	13	2.6	23	9	10.80	Nitrogen off				
14	2.3	26	8	7.84	14	2.5	24	9	8.95	13	2.5	24	22	^p
15	2.2	27	7	7.84	15	2.1	29	13	8.40	14	2.5	24	19	
Nitrogen off					Nitrogen off									
16	2.2	27	7		16	2.0	30	13		18	2.3	26	21	
17	2.2	27	7		17	2.0	30	11		23	2.4	25	17	
18	2.1	29	7		18	2.0	30	7		29	2.4	25	16	
19	2.3	26	8		19	2.5	24	9		32	2.8	21	11	
20	2.1	29	6		20	2.8	21	6		35	2.7	22	9	
21	1.6	37	5		21	3.4	18	5		36	2.8	21	9	
22	2.6	23	5		22	3.1	19	5		37	2.7	22	9	
23	2.4	25	5		23	3.6	17	5						
24	2.3	26	6		24	3.4	18	5						
25	2.2	27	8											
26	2.5	24	7											
27	2.7	22	6											
28	2.1	29	6											
29	2.2	27	6											
30	4.0	15	3											
31	3.6	17	3											

medullary centers, the shorter latent period at the return to air or oxygen is explained in part by the increased blood flow.

When anoxemia was produced by breathing nitrogen, the latent period for change in volume of breathing as estimated by the height of the respiratory curve ranged between 4 and 35 seconds. The average was 14.5 seconds. About 32 per cent of all cases have a latent period of 10 seconds or less, while in 29 per cent it was between 10 and 15 seconds. In the determinations of the volume of each breath by the Larsen spirometer the latent period ranged between 4 and 25 seconds, averaging 12.4 seconds. In almost all cases the latent period as estimated by this method was slightly less than that determined by the height of the respiratory curves.

The volume of breathing diminished quickly when the subject was restored to atmospheric air. The latent period as determined by the height of the pneumograph curve ranged between 3 and 34 seconds, averaging 6.9 seconds. A large number, 89.3 per cent, had a latent period of 10 seconds or less. This would indicate that the respiratory center, with respect to the volume of each breath responds to oxygen changes slightly earlier than the cardiac center.

The rate of breathing is increased by anoxemia when the fall in oxygen has become marked. On administering nitrogen the latent period for the increase in the rate of breathing ranged between 8 and 80 seconds, averaging 35.5 seconds. The normal rate of breathing ranged between 8 and 26 breaths per minute, and at the height of anoxemia it ranged between 11 and 46 breaths. The rate of breathing decreased more rapidly when the anoxemia was alleviated than it increased during the withdrawal of oxygen. The latent period for rate on the return to air ranged between 3 and 31 seconds, averaging 9.5 seconds. The respiratory stimulation due to low oxygen with respect to rate and depth passed away completely within from 10 to 53 seconds after returning to atmospheric air.

In a few cases which were kept at 380 mm. in the low pressure chamber we have determined the volume change when oxygen was administered. The per-minute volume of breathing was recorded in these experiments and the data are given in the table. It will be observed that the per-minute volume of breathing was much reduced even during the first minute of oxygen administration. A fall in rate was also present in four cases.

E. C. S.			B. R. L.			K. O. N.				
Minutes	Volume	Rate	Minutes	Volume	Rate	Minutes	Volume	Rate		
16	11.4	13	16	12.3	11	10	11.5	18		
17	11.6		17	11.9		11	11.6			
18	11.6		18	13.0		12	11.2			
19	12.8		19	13.3		13	11.5			
20	11.0		20	12.7		14	11.6			
21	11.9	14	21	13.9	12	15	11.1	18		
22	11.6		22	15.1		16	12.2			
Oxygen on			Oxygen on			17	11.7			
23	8.3	12	23	10.9	11	18	11.9	19		
24	6.1		24	5.8		19	14.6			
25	10.1		25	6.0		Oxygen on				
26	4.8		26	6.84		20	8.74		16	
27	7.7		27	8.4		21	7.61			
28	6.2		28	4.25		22	6.72			
						23	6.95			
						24	9.06			
						25	8.06			
G. S. M.			B. B. J.			B. R. L.				
Minutes	Volume	Rate	Minutes	Volume	Rate	Minutes	Volume	Rate		
14	11.9	12	12	11.5		15	11.9			
15	9.51		13	11.6		16	14.0			
16	10.1		14	12.5		17	13.1			
17	9.75		15	9.18		18	15.8			
18	12.2		16	13.2	23	19	14.1			
19	18.4	12	17	12.7	22	Oxygen on				
Oxygen on			Oxygen on			20	8.4	15		
20	14.0	11	18	9.51	15	21	5.60			
21	13.3		19	6.26		22	3.82			
22	11.3		20	8.28		23	3.36			
23	12.3		21	9.06						
24	10.7		22	6.16						
25	10.6		23	7.39						

Our data obtained from a study of men indicate that the respiratory center responds to a decrease in oxygen in the same manner and in about the same short time as Gasser and Loevenhart found in animals. The shortness of the latent periods both when oxygen is withdrawn and when it is administered, suggests that the oxygen effects are immediate

and determined only by the time required for the blood to pass from the lungs to the medullary centers. These data appear to lend support to the view that oxygen under certain conditions *per se* determines the condition of activity of the respiratory and other medullary centers.

In this connection the observations of Lindhard (17) are interesting because he found that an excess of oxygen diminished the excitability of the respiratory center. Kaya and Starling (18) made chloralized animals breathe a mixture of nitrogen and oxygen and found that a diminution of the oxygen from 20 to 14 per cent had, as a rule, no effect on the rhythm or depth of respiration, but that oxygen of 8 to 10 per cent increased the amplitude and rhythm of the respiratory movements. The short latent period that we obtained with nitrogen and in our respiration studies in the low pressure chamber and in rebreathing (1) indicates either that a man is more sensitive to changes in oxygen or that chloral alters the excitability of the respiratory center.

The quick responses made by the heart and the respiration to changes in the oxygen tension of the respired air make it appear that the oxygen has a direct influence on the excitability of the medullary centers which control the rate of heart beat and the breathing. Whether oxygen acts indirectly by increasing and decreasing the stimulating effects of carbon dioxide or whether oxygen itself, by the variation in partial pressure or in the rate of oxidation, is a stimulus to the medullary centers, still remains an unsettled question.

SUMMARY

1. The cardiac and respiratory medullary centers in man respond quickly to changes in the partial pressure of oxygen. A decrease in oxygen stimulates while an increase in oxygen inhibits the action of these centers.

2. The heart accelerated in from 5 to 55 seconds in response to a decrease in oxygen. In 66 per cent of all cases the acceleration began within 15 seconds or less. Administration of oxygen slowed the heart within from 5 to 30 seconds. In 86 per cent of the cases the retardation began within 15 seconds.

3. Changes in the partial pressure of oxygen in the respired air have a twofold action on the respiration; the rhythm and the depth of breathing may be altered. In a gradual and comparatively slow reduction in oxygen only the depth of breathing was usually increased. With a sudden decrease in oxygen the depth of breathing was first increased and later the rate.

4. The latent period for the increase in the depth of breathing in anoxemia ranged between 4 and 35 seconds, averaging 14.5 seconds. The latent period for the increase in the rate of breathing ranged between 8 and 80 seconds, averaging 35.5 seconds.

5. When the subject was returned to atmospheric air, the latent period for reduction in the volume of breathing varied between 3 and 24 seconds, averaging 6.9 seconds; for the rate of breathing it varied between 3 and 31 seconds, averaging 9.5 seconds.

6. In all subjects at a barometric pressure of 380 mm. (18,000 feet), administration of oxygen reduced the volume of breathing, and in some cases the rate also was decreased.

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EXPERIMENTAL STUDIES OF THE URETER

THE CAUSE OF THE URETERAL CONTRACTIONS

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INTRODUCTION

The first paper on the study of the ureter was devoted chiefly to an investigation of its movements and innervation, making use of ring preparations and the contractions of the ureters in situ, but the cause of the ureteral contractions received little attention. A number of experiments in this connection have been reported by other observers, but the conclusions reached do not accord.

Some investigators, such as Mulder, Donders, Mayer, Ludwig, Henderson, Lucas and others, consider distention of the ureter lumen by an accumulation of urine as the main cause of the contractions. On the other hand, Vallentin, Vulpian, Setschenow and others do not regard a certain amount of urine as a necessary condition for the development of spontaneous contractions, since they observed contractions which were produced by other measures, such as by stimulating ganglions of the abdominal and lumbar sympathetics. Although Engelmann obtained an augmentation of ureteral contractions in experimental animals after giving a large amount of fluid, yet he is inclined to consider the distention as neither the cause nor the causal condition of the contractions because first, no contractions were produced even by artificial distention of the ureter lumen; and second, normal movements of the ureter continued even in complete absence of urine secretion. Sokoloff and Luchsinger placed a whole ureter removed from an animal into normal salt solution, connecting both ends with cannulas. In their experiments an increase of the intra-ureteral pressure caused a corresponding acceleration in the rate of contractions, but if the pressure exceeded a certain maximum limit, the contractions ceased. Lewin and Goldschmidt also favor the theory that the ureteral contractions depend entirely upon the urine, which enters into the ureter and distends its lumen. Other clinical

observations in cases of ectopia vesicae by Slanski, Samschin, Greif-Smith and Feodrow throw no light on this question. Protopopow performed a series of experiments on the ureteral contractions under various circulatory and secretory conditions of the kidney, and also after injecting several fluids into the renal pelvis. He reached the conclusion, from these experiments, that the passing of the urine through the ureter lumen is not a necessary condition for spontaneous ureteral contractions, although it has a definite influence upon the contraction rate.

METHODS

The experiments were carried out by two methods. Dogs were used, and after anesthesia by morphin and ether, were so firmly fixed on a holder that movement was impossible.

In the first method the left abdominal cavity was opened obliquely from a point which lay at the lower border of the last rib nearly two inches laterally from the linea alba, to the symphysis pubis. This incision ran almost parallel to the course of the left ureter. An additional incision a few inches long was made along the last rib, starting at the upper end of the sagittal incision toward the outer side. The intestines were drawn into the right half of the abdominal cavity, and the abdominal wall was covered with an electric pad to prevent cooling of the viscera. In this way the left ureter together with the left kidney and the bladder could be seen, and the abdominal cavity was opened so widely that the ureter was not influenced by any respiratory or circulatory movements of other parts of the body. Usually the spontaneous peristalsis of the ureter continued for a few minutes only. After opening the bladder a small cannula (outlet cannula) was introduced into the orifice of the left ureter, the urine flow through the cannula being recorded by a drop tambour. A long, thin venous cannula was led to the renal pelvis of the same side through the kidney parenchyma, by means of which various solutions were injected into the ureter lumen (inlet cannula).

Although both ends of the ureter were connected water-tight with two cannulas, the nerves and blood supply which come up to the ureter from the kidney and the bladder were little injured by this method, the ureter remaining in a relatively normal condition except for direct exposure to the air. The left abdominal cavity, thus made almost empty, was heated from a distance by a nitrogen lamp to a temperature of nearly 38°C. To keep the ureter moist, a small amount of Locke's

solution was poured into the abdominal cavity. A point of the ureter was connected to a lever with a small hook, whereby a small section adjacent to this point was suspended in the shape of an inverted V. As a peristaltic contraction passed through this point, this section was stretched in a straighter line, pulling the lever downward, the other end of the lever tracing a curve on a revolving drum. Curves obtained by these methods, therefore, represent contractions of the longitudinal muscles of the ureter. But in the ureter in situ both contractions of the longitudinal and the circular muscle layers occur at the same time, so that the curves can be regarded as representing, in time, contractions of the circular muscles. This conclusion is corroborated in the present experiments by the fact that the urine flow was blocked during the peristalsis, which caused a closure of the ureter lumen by the contraction of the circular muscle. By this method the experimental results 1 to 7 were obtained.

In the second method the dog was laparotomized by an incision nearly five inches along a line running laterally and upward from the symphysis pubis on the left side of the abdominal wall. The lower end of the ureter was connected with an outlet cannula in the same manner as in the first method; the kidney and the upper half of the left ureter remained in the natural condition and were protected against exposure to the air, yet movements of the body due to respiration and circulation were occasionally transmitted to the lever, which to a great extent spoiled the true curves of the ureteral contractions. A point of the ureter also was suspended to the lever and several fluids were injected into the femoral vein. By this method experimental result 8 was obtained.

EXPERIMENTAL RESULTS

1. Injection of 0.9 per cent salt solution into the renal pelvis: With a low pressure of injection the ureter, which previously had no spontaneous contractions, began to register a few contractions per minute. Fluid from the outlet cannula disappeared during the course of a peristaltic wave through the length of the ureter. The rate of contractions then increased approximately proportional to the raising of the pressure to a certain limit. But with a pressure higher than that limit no contractions were observed, the solution flowing more rapidly and uninterruptedly.

2. Injection of 1 per cent urea solution into the renal pelvis: This also caused a definite increase in ureteral activity. The rate of the

contractions, however, was greater than that caused by injecting salt solution at the same pressure, the number of contractions being at least one and a half times as many in comparison. Occasionally tonic contractions occurred and the outflow of fluid ceased for a rather long interval of time. By injecting salt solution after urea, the ureter showed less irritation, there being noticed a series of separated contractions, fewer in number, and no tonic contracture.



Fig. 1. Portion of graphic tracing obtained in experiment of July 7, 1919. Upper record, contractions of the ureter. Middle record, urine flow. Lower record, base line and time record in minutes. 1, injection of salt solution. 2, injection of urea solution (1 per cent).

3. Injection of a saturated uric acid solution into the ureter lumen: This solution produced an acceleration in the rate of contractions almost equal to that caused by the urea solution. But tonic contractures were observed, greater in number and longer in duration than after injection of the urea solution.



Fig. 2. Portion of graphic record obtained in experiment of July 3, 1919. Upper record, ureteral contractions. Middle record, urine flow. Lower record time in minutes. A, injection of uric acid solution (saturated); ↑, death of animal; 1, 2, 3, injections of salt, uric acid and urea solutions respectively.

4. Injection of urine of the respective animals into the renal pelvis: The urine exerted a distinctly favorable influence upon ureteral activity, contractions being more frequent than after salt solution. They presented, however, less tendency to tonicity. Salt solution after urine lessened the contractions.

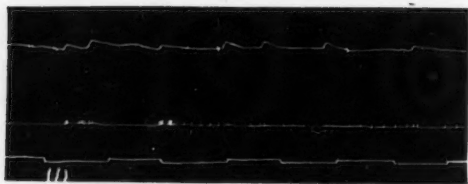


Fig. 3. Portion of graphic record obtained in experiment of June 23, 1919. Upper record, ureteral contractions. Middle record, urine flow. Lower record, time in minutes. 1, injection of urine into the renal pelvis.

5. Injection of glycerin-water mixture and cod liver oil into the ureter lumen: For the purpose of deciding whether the viscosity of fluids which pass through the ureter lumen has any effect upon the movements of the ureter, glycerin in various concentrations and cod liver oil were injected into the renal pelvis. A weak solution of glycerin (5 per cent) had the same effect as salt solution. An increasing concentration gave no distinct acceleration of the contractions, either in rate or in force. The injection of cod liver oil did not produce the augmentation caused by urea or uric acid solutions.

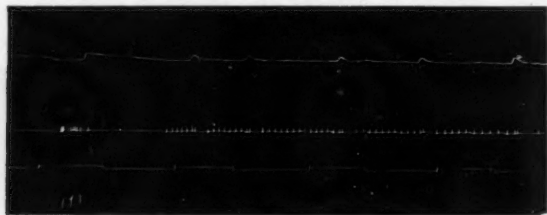


Fig. 4. Portion of graphic record obtained in experiment of June 23, 1919. Upper record, ureteral movements. Middle record, urine flow. Lower record, time in minutes. 1, injection of glycerin water mixture.

6. Injection of drugs into the ureter lumen: In the previous paper the effects of adrenalin, physostigmin and atropin upon ring preparations were described. These drugs were employed also in the present experiments, and their effects on the ureter in situ were the same as upon the excised ureter. Adrenalin caused marked rapid movements with no pause between them, but no increase in tonus. Physostigmin also produced an augmentation in rate of contractions together with a

slight increase in tonus. Atropin exhibited a gradual decrease in force to a final disappearance of contractions, though it seemed to affect the rate of contraction very slightly.



Fig. 5a



Fig. 5b

Fig. 5, a. Portion of graphic record obtained in experiment of July 1, 1919. Upper record, ureteral contractions. Middle record, urine flow. Lower record, time in minutes. 1, adrenalin injection (1 to 1,000,000).

Fig. 5, b. Portion of graphic record obtained in experiment of July 1, 1919. Upper record, ureteral movements. Middle record, urine flow. Lower record, time in minutes. 1, injection of physostigmin (1 to 200,000).

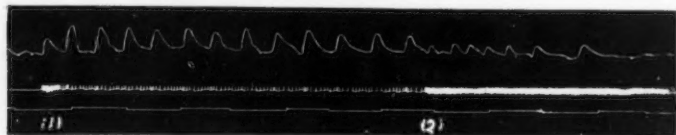


Fig. 5, c. Portion of graphic record obtained in experiment of July 1, 1919. Upper tracing, ureteral contractions. Middle record, urine flow. Lower record, time in minutes. 1, atropin injection (1 to 400,000). 2, injection of the drug with a higher pressure.

7. Injection of sand-water mixture into the ureteral lumen: Even with a very low pressure, at which salt solution produced only a few contractions per minute, the ureter contracted in a tonic manner, its tone increasing markedly and contractions following successively with no interruption. A larger amount of the mixture caused a strong con-

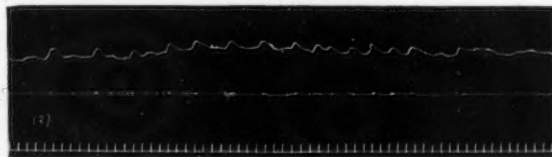


Fig. 6. Portion of graphic record obtained in experiment of July 7, 1919. Upper record, ureteral movements. Middle record, urine flow. Lower record, time in minutes. 2, injection of sand-water mixture.

tracture of the ureter, only a few drops of the fluid being expelled from the outlet cannula. The circular muscle layer seemed to be especially stimulated, so that the ureter was put in a condition of vermicular movements, which continued to travel up and down its different sections.

8. Injection of salt solution and urea intravenously: Five to ten minutes after injecting 50 to 100 cc. of 0.9 per cent salt solution into the femoral vein, drops of urine appeared at a certain rate, sometimes accompanied by a number of distinct contractions, again, the ureter remaining perfectly quiescent. The urea injection (1.0 gm. in 10 cc. solution) presented nearly the same effect, contractions, however, being slightly more in number and stronger in force.

From these experiments definite evidence is obtained in the first place, that the distention of the ureter lumen produces contractions. This was again proved in an experiment in which the outlet cannula was clamped off to prevent the flow of urine for a while, so that the intra-ureteral pressure was very much heightened. In response to this increase of pressure, the ureter began to contract after a short period of time and showed an increase of activity, the tonus and amplitude being heightened with each contraction until the outlet cannula was again opened. This fact indicates clearly that the distention of the ureter lumen by an accumulation of urine secretion may be an important cause of ureteral contractions.

In the second place, it is probable that the urine may exert a chemical influence upon the ureteral movements. It is for the purpose of studying this point that urea and uric acid were injected into the renal pelvis through the inlet cannula. As stated above it was found that urea and uric acid solutions caused a more vigorous activity of the ureter than a neutral solution (salt solution) under the same distention of the ureter lumen. The ureter also contracted more frequently when the normal urine of the animals was injected. The peristaltic contractions of the ureter, therefore, depend not only upon the mechanical distention of the ureter lumen, but also, to a certain extent, upon the composition of the urine.

It is a noteworthy feature that these agents, when applied only on the mucous surface of the ureter, affect its movements. This fact implies that the contractions of the muscle layer must be brought about in a reflex manner, stimulus of the sensory nerves of the mucosa being transmitted by the ganglion cells to the motor nerves of the muscles, which then are thrown into a condition of contractions. Occa-

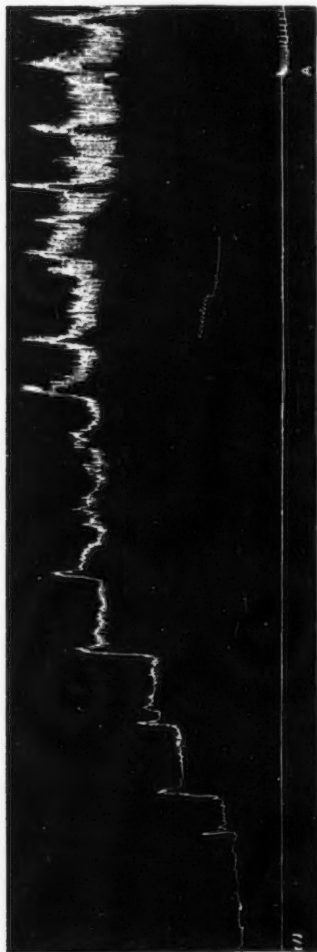


Fig. 7. Portion of graphic record obtained in experiment of June 9, 1919. Upper record, ureteral movements. Middle record, urine flow. *I*, injection of 50 cc. of salt solution intravenously. *A*, opening of outlet cannula.

sion was had in one of the experiments to corroborate the truth of this conclusion: It was observed that after the death of the animal contractions could be obtained by irrigating the ureter with the different solutions described, but under these conditions the contractions were the same in rate and form in spite of the injection of different fluids such as salt, urea, uric acid solutions and urine. The experiment indicates that in the absence of certain nervous actions, injection of various fluids effects merely a mechanical distention of the surviving muscle layer and produces its contractions in consequence of this factor alone. Further, the vigorous tonic contracture caused by injecting sand-water mixture, which may be regarded as a result of stimulation by solid bodies acting on the mucous surface, may be considered as definite proof that there is a reflex mechanism in the development of the ureteral peristalsis.

Under normal conditions distention should be regarded as acting in part directly on the muscle and in part as causing a reflex contraction. This conclusion is indicated at least by the fact that in some of the experiments the ureteral contractions after the death of animals were strikingly different in rate and shape from those obtained in life, the former being quicker in duration and slower in rate than the latter. This difference depends probably upon the absence of the nervous factor. By distention the sensory nerves of the ureteral wall are probably stimulated and thus have a reflex effect upon the muscular layer, initiating or modifying the resulting contraction.

DISCUSSION

As generally accepted, the ureter may be considered as having the power of independent contraction to a relatively great extent. When the muscle layer is kept in a sufficiently tonic condition, its contractility is manifested in visible contractions. This tonic condition of the ureter sufficient to support contraction is brought about by various mechanisms, such as nervous control, either by direct stimulation of the motor nerves (as the author has shown in the first paper) or by way of a local reflex, by mechanical stretch of the muscle fibers themselves, by direct chemical effect upon the muscle tissue (as excised ureter in Locke's solution), etc. In the natural position of the organ the nervous networks of its wall probably keep it in such a tonic condition that an additional slight increase of the tone—for instance, by distention of the lumen or by chemical influence of urine—can cause its contractions.

After opening the abdominal cavity its tone is very much lessened, probably because of different circulatory conditions of the ureter, loss of temperature and other circumstances, so that the contractions cease after a short interval of time. If the tone, however, is restored to a sufficient degree to cause contractions either mechanically by great distention of the lumen, which effects a stretching of the muscle fibers, or chemically by drugs, which act reflexly, the ureter begins to contract again and goes on while these effects continue. On the other hand, if the motor nerve is stimulated adequately to keep the ureter in sufficient tonus, its contractions may take place even in an absence of other factors, as was practically observed by some authors and the writer.

The ureteral movements, therefore, are produced by various mechanisms,—such as stimulation of the motor nerves, distention of the lumen, chemical effect of the urine,—each of which may, alone, cause contractions of the ureter or which may coöperate with one another.

CONCLUSIONS

1. Distention of the ureter lumen causes the development of contractions, which increase to a certain limit with an increase in pressure.
2. The chemical composition of the kidney secretion may also effect the development of ureteral contractions, by means of a reflex action.
3. The viscosity of the fluids which pass through the ureter lumen affects the contractions only to the slightest degree. Solid bodies, such as a calculus, however, produce vigorous tonic contractions.
4. The peristalsis of the ureter should be referred not to one, but to several factors, which act mainly in coöperation, but which vary in value under various conditions.

THE EFFECTS OF INCREASING THE INTRACRANIAL PRESSURE IN RABBITS

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In a series of "heat puncture" experiments with rabbits (1) the results were at times complicated by convulsions and death. It was thought possible that the symptoms and death in these cases might be due to an increase in the intracranial pressure. To throw light on the subject the general question of the effects produced by increasing the intracranial pressure is being studied. The present paper gives a preliminary report of the investigation.

A number of early workers report the results of experimentally increasing the pressure in the cranial cavity by cerebral compression in animals; and also of clinical cases of traumatic cerebral lesions. The latter, in fact, comprise the bulk of the evidence. Horsley (2) was interested in the subject from a clinical point of view. Using dogs, he increased the intracranial pressure by means of a rubber bag distended with mercury and found that a definite increase always resulted in death, which he interpreted to be due to an arrest of the respiratory movements. Release of the pressure and artificial respiration were effective in the recovery of the animals. Cushing (3) obtained similar results but ascribed death to a paralysis of the vasomotor center in the medulla subsequent to a prolonged stimulation of the center causing a marked rise (250 mm. Hg.) in blood pressure.

More recently Dixon and Halliburton (4) using a method somewhat similar to that of Horsley (2) obtained detailed results of moderate and great changes in the cerebrospinal pressure in dogs. They increased the pressure by forcing Ringer's solution into the craniospinal cavity through a cannula in the subcerebellar cisterna. Moderate degrees of compression, as 80 mm. of mercury, applied for a few seconds produced effects clearly due to stimulation of the principal bulbar centers. The heart was slowed by vagus stimulation, the blood pressure raised by stimulation of the vasomotor center, and the respiration rate,

sometimes initially increased, but always finally diminished. When the pressure was above the arterial pressure (300 to 400 mm. of mercury) respiration ceased in a few seconds; while blood pressure rose rapidly if artificial respiration were used until the vagus and finally the vasomotor center became paralyzed. On removal of the compression the centers recovered in the reverse order. Death always followed pressures of 80 mm. of mercury or more applied for only a few seconds unless artificial respiration was resorted to.

Cannon (5) obtained somewhat similar results with cats. Increasing the intracranial pressure by concussion caused cessation of respiration. Cannon (5) also, in reporting clinical findings in cases of brain lesions, states that there is generally evidence of a rupture of the intracranial blood vessels and changes in the osmotic condition of the brain substance causing a rise in intracranial pressure. The symptoms are unconsciousness, coma, clonic spasms, labored breathing, slow heart beat, rise in body temperature and death unless decompression is resorted to; all analogous to those produced by experimentally increasing intracranial pressure in animals. The clinical symptoms are reported in many other cases by numerous observers.

There are no data in the literature on the effect of increasing the intracranial pressure in rabbits. The evidence reported in the present paper, although incomplete as yet, is being extended.

The symptoms preceding death in the fatal cases of "heat puncture" were so markedly similar to those produced by experimentally increased intracranial pressure and to clinical findings, that an attempt was made to prove that the cause of death was the same in all these cases. In order to do this the conditions during "heat punctures" were controlled so as to insure a pressure in the cranial cavity comparable to that produced artificially or by brain lesions. The cylinder used in puncture experiments to hold the puncture needle was screwed firmly into the trephine opening in the skull and the hole closed tightly by the puncture needle or other means so that any pressure due to intracranial hemorrhage or changes in the brain substance would result in an actual increase in the pressure in the cranial cavity. Because of the impossibility of passing a needle through the dura, cortex, and into the corpus striatum without rupturing small blood vessels, autopsies almost invariably showed some degree of hemorrhage which would be sufficient to raise the pressure to some extent.

Artificially produced pressure in the cranial cavity was produced by means of a metal cylinder screwed firmly into the trephine opening

in the skull, the opening having been made without injury to the dura. In the cylinder was securely fastened a metal tube 4 mm. in diameter and 3 or 4 cm. in length, to which was fastened a rubber tube connected with a bulb by means of which air could be forced into the opening in the skull, increasing the pressure within the cavity. The tube and bulb were both connected with a mercury manometer which recorded the pressure used. The method was varied in certain experiments by using a rubber bag inserted through the cylinder into the trephine opening in the skull. In some cases the bag was distended with 5 to 10 mm. of mercury and the opening closed; in others the mercury was run into the bag from a burette, so that the pressure applied could be accurately gauged by the height of the column of mercury.

The symptoms produced were the same with each method. A pressure of 30 to 40 mm. of mercury (272 to 408 mm. of water) or more applied one to three minutes caused, at first, increase in the rate of respiration followed by a decrease, a slowing of the heart rate, vasoconstriction, dilatation of the pupils, short clonic spasms probably due to asphyxiation and, finally, a cessation of respiration. If, at this stage, the pressure was immediately released, the respiration was again resumed and the other symptoms passed off. Application of the pressure again for only a few seconds caused a repetition of the above, release again bringing recovery. This may be repeated a number of times, but if the pressure was applied for more than a few seconds after respiration ceased, recovery was impossible without the use of artificial respiration.

Twelve experiments were performed on rabbits, using fatal pressures 20 to 30 mm. of mercury, (272 to 408 mm. of water) with similar symptoms and death occurring in every case in which the pressure was applied for a sufficient length of time, generally from one to three minutes.

Twenty-three experiments on rabbits showed that a moderate increase, 15 mm. of mercury or less, (200 mm. of water) in intracranial pressure produces less marked effects, increase in the rate of respiration and vasoconstriction with a subsequent rise in body temperature. This phase of the subject is being further investigated.

The symptoms following the "heat punctures" in which care was taken to have the puncture hole securely closed so that an increase in the pressure in the brain case was possible, were in general comparable to those just stated for artificially increased pressure. The pressure symptoms, in most cases, occurred two or three hours after the "puncture" operation. There was an increased rate of respiration followed by slow, labored breathing, slow heart beat, dilatation of pupils, vaso-

constriction, and generally a rise in body temperature. Clonic convulsions of short duration soon came on, followed by a fall in temperature just prior to death. In some cases the pressure effects occurred earlier (within one-half to one hour); in others later, five to ten or even twelve hours after the operation. Death could be prevented by a decompression operation; that is, by making a small opening in the skull or by removing the puncture needle or cylinder thus preventing the increase in pressure within the brain case. The symptoms occurred only in those cases in which no opening was left in the skull; and, of the thirty cases of puncture in which there was definitely no opening left, twenty-eight showed pressure symptoms followed by death. There were also twenty-four other cases of puncture with fatal pressure symptoms which occurred early in the series and of which no record was kept in regard to the opening in the skull. None of the twenty punctures with the cylinder or needle definitely removed, or with an extra opening in the skull, showed any of the effects of increased pressure in the brain cavity except possibly a rise in body temperature.

Since fatality and the preceding effects are noted only when the brain cavity is kept air-tight by eliminating any opening in the skull, thereby allowing the possibility of an increased pressure in the cranium, in case of hemorrhage or increased brain volume they would seem not to be due directly to the puncture operation but rather to an increased intracranial pressure. Also, the symptoms accompanying death are so like those induced by artificially increasing the pressure and by brain lesions that this conclusion seems justified.

The explanation of the cause of the fatal symptoms is the same as that offered by Dixon and Halliburton (4). The increased pressure at first acts as a stimulus to the bulbar centers and finally, when continued, causes paralysis of the same centers, that of respiration being the first to be affected. The stimulation effect is evidenced by the early increase in the rate of respiration by stimulation of the respiratory center, by the slowing of the heart rate through the cardio-inhibitory center, by vasoconstriction through the vasomotor center, and by dilatation of the pupils through the cervical sympathetic nerve. Over-stimulation, as would be expected, brings about a paralysis of the same centers and a cessation of their functioning.

The fatal pressure recorded for rabbits, 20 mm. of mercury (272 mm. of water) is considerably lower than that found by Dixon and Halliburton (4) for dogs. The difference is probably due to the higher blood pressure in dogs, and to the difference in the method used in raising the intracranial pressure, and place of application of the pressure.

SUMMARY

Increasing the intracranial pressure in rabbits, 20 mm. of mercury (272 mm. of water) or more, results in accelerated respiratory movements followed by their cessation, slow heart beat, vasoconstriction, dilatation of the pupils, spasms of asphyxiation, and finally death within one to three minutes unless artificial respiration is used or the pressure is released.

Moderate degrees of pressure, 15 mm. of mercury (200 mm. of water) or less cause increase in the rate of heart beat, vasoconstriction and a rise in body temperature.

The pressure symptoms and death following "heat puncture" operations were found only when no opening was left in the cranium; and, by comparison with the symptoms attending artificially increased intracranial pressure and clinical cases of brain lesions, seem to be due to the same cause.

The cause of death, and the preceding symptoms, when the intracranial pressure is raised appears to be stimulation followed by paralysis of the principal bulbar centers.

The author wishes to express her gratitude to Prof. S. S. Maxwell for his advice in this investigation.

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ON THE DISTRIBUTION OF THE NON-PROTEIN NITROGEN IN CASES OF ANAPHYLAXIS AND PEPTONE POISONING

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Since Richet (1) in 1902 first studied the problem of anaphylaxis systematically, a number of investigators have worked on similar lines and advanced various theories to explain why the lesion and symptoms of anaphylaxis take place after protein has been injected into an animal previously sensitized with the homologous serum.

I do not wish to give a detailed description, only stating that there exist two theories of anaphylaxis, namely, the humoral or chemical theory and the cellular one. The former, as many authors (2), especially Friedberger (3) have pointed out, ascribed the source of anaphylaxis to the protein poison produced from the products of a reaction between free or circulating anaphylactic-antibody and antigen by the action of a complement. Although there is some diversity of opinion as to detail, i.e., whether the protein that is broken down is the protein injected, as Vaughan and Friedberger (2) claimed, or the protein of the sensitized animal itself, as was reported by Friedemann (4), Pfeiffer and Mita (5), Jobling and Peterson (6), yet they are fundamentally in agreement in that they believe that a protein poison is responsible for the anaphylaxis. This theory of anaphylaxis is supported by a mass of experimental data especially *in vitro*, bearing on the production of the protein poison. According to the second theory it is believed that the antibody is within the cells and the antigen-antibody reaction occurs in this place rather than in the blood stream.

Weil (2) who emphasized the cellular theory most strongly held that anaphylactic shock has no relation to the chemical poison but rather is a transitory shock as the result of a reaction between the cellular antibody and the circulating antigen. From the fact that there was no evidence of the protein poison in his transfusion experiments, he concludes that the phenomenon is attributable to the cellular reaction involving the hepatic parenchyma (7).

The question as to which theory is more plausible, the humoral or the cellular one, must be determined by further studies.

Zunz and György (8), who examined the alternation of the blood nitrogens, stated that there is a definite increase in amino-acids during acute shock in dogs. Jobling and Peterson (6) found that the acute shock is accompanied by an increase in non-coagulable nitrogen of the blood in addition to that of the amino-acids.

Recently Whipple and Van Slyke (9) have reported their detailed investigation on the influence of the proteose intoxication upon the nitrogenous products of the blood, pointing out that the acute shock following an injection of a toxic proteose is usually associated with a large increase in the non-protein nitrogen of the blood, chiefly in the blood urea nitrogen, and also with small increases in the amino and peptiden nitrogens. Keeping these results in mind my investigation was carried out to determine whether this would be the case also in anaphylaxis as in proteose intoxication.

METHOD

Guinea pigs weighing 200 to 400 grams were employed in all experiments. In order to avoid the possible influence of diet upon the nitrogenous constituents of the blood, the pigs received no food for about twenty-four hours previous to being bled. The animals were exsanguinated in all cases by opening the carotid artery and the blood was quickly defibrinated with a stirring rod. The blood thus obtained from three or four pigs was thoroughly mixed and urea nitrogen, total non-protein nitrogen and amino-acid nitrogen were determined.

1. *Urea nitrogen.* Van Slyke and Cullen's method (10) was employed, using methyl-alcohol as a substitute for octhyl-alcohol.

2. *Total non-protein nitrogen.* After removal of the protein by the heat-caolin method (sometimes heat-trichloroacetic acid method was used) the micro-Kjeldahl method of Folin and Farmer (12) was employed, the ammonia being titrated with 0.02N acid and 0.01N alkali, using methyl-red as an indicator.

3. *Amino nitrogen* was estimated by Van Slyke's method, the protein being removed by Okada's heat-caolin method (12).

The guinea pigs were divided into three groups. In the first, pigs which had not been submitted to any experimental procedure were used as controls. In the second, 2 cc. of 10 per cent peptone (Witte) solution per 100 gram of body weight were administered intraperitoneally to

TABLE 1
Contents of blood nitrogen of normal guinea pigs

EXPERIMENT NUMBER	GUINEA PIG	TOTAL NON- PROTEIN NITRO- GEN	NON-PROTEIN NITROGEN PER 100 CC. OF BLOOD AS		
			Urea	Non-urea	Amino nitrogen
	<i>grams</i>	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>
I	1. 320	57.6	36.4	21.2	
	2. 365				
	3. 284				
II	4. 396	53.1	33.2	19.9	
	5. 252				
	6. 374				
III	7. 380	64.5	38.4	26.2	5.7
	8. 410				
	9. 342				
IV	10. 274	55.8	29.2	26.6	5.9
	11. 360				
	12. 255				
V	13. 294	59.8	37.1	22.7	5.6
	14. 290				
	15. 320				
VI	16. 353	55.0	28.9	25.1	
	17. 297				
	18. 377				
VII	19. 294	57.3	33.2	24.1	5.1
	20. 360				
	21. 256				
VIII	22. 405	56.3	34.1	22.2	5.4
	23. 335				
	24. 200				
IX	25. 345	59.9	36.7	23.2	5.1
	26. 376				
	27. 238				
X	28. 198	56.0	31.3	24.7	4.9
	29. 307				
Average		57.5	33.9	23.6	5.4

TABLE 2
Blood nitrogen in peptone poisoning

EXPERIMENT NUMBER	GUINEA PIG	RESULTS	TIME AFTER INJECTION	TOTAL NON- PROTEIN NITROGEN	NON-PROTEIN NITROGEN PER 100 CC. BLOOD AS		
					Urea	Non- urea	Amino nitro- gen
	grams		hours	mgm.	mgm.	mgm.	mgm.
I	1. 400	Moderate symptoms	6	82.3	53.3	29.0	6.8
	2. 320	Moderate symptoms					
	3. 250	Severe symptoms					
II	4. 300	Moderate symptoms	4	71.4	44.3	27.1	6.0
	5. 360	Moderate symptoms					
	6. 352	Moderate symptoms					
III	7. 360	Severe symptoms	6	77.1	48.7	28.4	6.7
	8. 286	Moderate symptoms					
	9. 254	Moderate symptoms					
IV	10. 304	Moderate symptoms	5	89.6	52.8	36.8	9.3
	11. 332	Severe symptoms					
	12. 264	Died in 3 hours					
	13. 300	Moderate symptoms					
V	14. 316	Moderate symptoms	5	74.2	46.2	28.0	7.8
	15. 352	Moderate symptoms					
	16. 360	Mild symptoms					
	17. 320	Moderate symptoms					
VI	18. 240	Severe symptoms	6	85.4	52.4	33.0	6.2
	19. 280	Moderate symptoms					
	20. 312	Moderate symptoms					
	21. 268	Moderate symptoms					
VII	22. 315	Moderate symptoms	4½	84.6	53.0	29.8	7.0
	23. 280	Died in 2 hours					
	24. 340	Severe symptoms					
VIII	25. 200	Severe symptoms	6	79.9	46.7	33.2	7.1
	26. 226	Severe symptoms					
	27. 200	Moderate symptoms					
	28. 190	Severe symptoms					
IX	29. 200	Severe symptoms	4½	73.5	42.9	30.6	
	30. 216	Died in one hour					
	31. 205	Moderate symptoms					
	32. 240	Severe symptoms					
Average				79.8	48.9	30.7	7.1

TABLE 3
Blood nitrogen in anaphylactic shock

EXPERIMENT NUMBER	GUINEA PIG	RESULTS	TIME AFTER INJECTION	TOTAL NON- PRO- TEIN NITRO- GEN	NON-PROTEIN NITROGEN PER 100 CC. BLOOD AS		
					Urea	Non- urea	Amino- nitro- gen
	<i>grams</i>		<i>hours</i>	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>	<i>mgm.</i>
I	1. 264	Severe symptoms	6	101.2	67.7	33.5	6.7
	2. 272	Mild symptoms					
	3. 268	Severe symptoms					
	4. 212	Severe symptoms					
II	5. 252	Severe symptoms	6	85.7	55.6	30.1	7.3
	6. 220	Moderate symptoms					
	7. 212	Moderate symptoms					
	8. 204	Severe symptoms					
III	9. 340	Severe symptoms	5	106.5	74.3	32.2	7.8
	10. 288	Severe symptoms					
	11. 312	Severe symptoms					
	12. 288	Severe symptoms					
IV	13. 384	Mild symptoms	5½	79.2	48.7	30.5	6.9
	14. 272	Mild symptoms					
	15. 394	Severe symptoms					
V	16. 196	Died in 2 hours	3	82.7	53.5	29.2	
	17. 204	Died in 3 hours					
	18. 200	Severe symptoms					
VI	19. 392	Moderate symptoms	6	69.3	40.6	28.7	7.0
	20. 396	Moderate symptoms					
	21. 380	Severe symptoms					
VII	22. 204	Died in 2 hours	5	77.5	45.3	32.2	
	23. 200	Died in 1 hour					
	24. 225	Severe symptoms					
VIII	25. 340	Severe symptoms	5	99.5	63.3	36.2	9.2
	26. 280	Severe symptoms					
	27. 310	Moderate symptoms					
	28. 326	Severe symptoms					
IX	29. 376	Moderate symptoms	6	70.1	42.0	28.1	6.9
	30. 256	Severe symptoms					
	31. 250	Severe symptoms					
Average				85.4	54.6	31.2	7.4

each pig. In the third group, the animals were sensitized with 0.02 cc. serum and after an interval of 2 or 3 weeks, 1 cc. of the same serum as in the case of group 2, per 100 gram body weight, was injected intraperitoneally. The results are shown in tables 1, 2 and 3.

It is seen from table 2 that the peptone intoxication is accompanied by a marked increase in the non-protein nitrogen of the blood. The urea nitrogen is materially increased. The other non-protein nitrogenous constituents—in our cases non-urea and amino nitrogen—have also shown more or less increases. These results may be in accord with those of experiments with dogs performed by Whipple and Van Slyke who concluded that this increase in non-protein nitrogen is a result of an abnormally rapid tissue autodigestion caused by the action of a toxin (9).

As to anaphylaxis, as indicated in table 3, it has the same influence upon the non-protein partition of the blood as peptone poisoning or rather it appears to be more intense. From these results it appears probable that in anaphylaxis, as in peptone shock, rapid autolysis of the tissue protein may occur and thus lead to the same chemical changes in the animal body. Jobling and Peterson (6) have interpreted their finding as indicating "the cleavage of serum proteins (proteoses) through the peptone stage to amino-acids, and an intoxication by these peptones with a resulting cellular injury." I should not like to conclude from the results of my experiments whether it may be the peptone-like split products, as Jobling and others have maintained, which give rise to such a process and other symptoms in anaphylaxis, or whether it may be, as Weil (7) reported, the result of such hepatic lesions as are seen in poisoning by chloroform or phosphorus which involves the function and structure of that tissue. The problem must remain to be solved by further researches.

SUMMARY

1. Peptone intoxication is associated with a marked increase in urea nitrogen and also more or less in non-urea and amino nitrogen, thus confirming the results which have been reported by Whipple and Van Slyke.

2. The changes in the nitrogenous constituents of the blood in anaphylaxis are similar to those of peptone intoxication but more intense.

3. Anaphylaxis as well as peptone intoxication lead to an abnormally rapid autodigestion of tissue protein. The causative factors, as yet undetermined, are probably the same in both cases.

I wish to acknowledge my indebtedness to Prof. Dr. S. Mita for his suggestions and kind advice in carrying out this work, also to Prof. Dr. K. Katayama for his encouragement.

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THE EFFECT OF QUININE ON THE NITROGEN CONTENT OF THE EGG ALBUMEN OF RING-DOVES

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v. Noorden (1) observed in mammals that prolonged dosage with quinine was accompanied by a marked diminution of the nitrogenous bodies which appeared in the urine. He concluded that under such prolonged dosage the nitrogen of the food and tissues is not dissipated so rapidly but is somehow conserved or stored in the body. In this laboratory Riddle and Anderson (2) investigated the following subject: When the body of a ring-dove produces eggs it separates from itself a large amount of protein for the formation of the egg-white and egg-yolk. Does the presence of quinine in the organism at the time of egg-formation affect the amount of protein which the body yields to the egg? From that investigation it was concluded that the *amount* or volume of albuminous substance expended by the body in the production of egg-white (and probably also of egg-yolk) is decreased under quinine. v. Noorden's conclusion was thus confirmed and one tissue or organ—the oviduct—was identified as a specific part of the body which shares in the conservation of nitrogen under quinine.

Riddle and Anderson studied only the relative amounts or quantities of albuminous material produced under dosage and made no determinations of the actual amount of nitrogen present in the normal and treated egg albumens.¹ They state (p. 99):

Whether there was an actual reduction of the nitrogen present is not definitely shown by our data since it is conceivable, even though not at all probable, that the reduction occurred only or chiefly in the amount of water present in the albumen.

¹ Evidence was obtained (p. 100) indicating that in the egg-yolks the relative proportions of protein and lipoid were unchanged; the absolute amounts of both being diminished.

To learn definitely whether and how the nitrogen is affected in such egg albumens was the purpose of the present study. It may be stated at once that the result of this study shows that under quinine the amount of the egg albumen decreases; and that this diminished quantity certainly contains a smaller amount of nitrogen and a higher percentage of water than the normal albumen.

MATERIAL AND METHODS

Seven of the eleven birds used by Riddle and Anderson (2) were used for the present study. These birds were blond and white ring-doves and hybrids of these two forms. They were all a year older than at the time of the earlier experiment and for our purposes were, of course, being subjected to a second period of dosage. The advantages of using the same birds and at the same season of the year, and weighing and analyzing approximately the same number of clutches of eggs, are obvious. It should be noted, however, that previous dosage may have had some lasting effects on the birds and that it is perhaps too much to expect all of the birds precisely to duplicate the situation observed in the previous experiment.

The birds were all freely laying females, each penned with its own male mate. Pairs of eggs were usually obtained from each female at intervals of seven to ten days. The quinine was administered in the form of gelatin-coated quinine sulfate pills. The dosage, $\frac{1}{4}$ grain at first and $\frac{1}{2}$ grain later, was given twice daily—in the early morning and the late afternoon. During a period of four days following the laying of the first egg of the pair or clutch the dosage was omitted, as had been done in the earlier experiment, in order that the eggs might not be broken and the beginning of growth of the succeeding pair of yolks not too greatly delayed. Dosage was begun in March. The date of change of dosage (to $\frac{1}{2}$ grain twice daily) varied slightly, but for most birds was about May 4. No blank dosing was considered necessary with these very tame birds, since earlier work had shown that the effect of handling is negligible.

The accurate weighing of the albumen, essential alike to accurate comparisons of the gross amounts of albumen produced and to a determination of percentage nitrogen based on per gram solids (see below) presents considerable difficulties and some possible inaccuracies.²

² During its passage down the oviduct the yolk is continually absorbing water from the albumen (Spohn and Riddle, (3) p. 405). After laying this loss continues and a further loss of water from the albumen to the air begins. The best that

Omitting any extended statement on these difficulties, however, we may note that the method adopted was to weigh the whole egg as soon as possible after laying,³ steam it for eight minutes, cool in cold water for four, dry the shell and rapidly separate the yolk and egg-white with a clean blunt spatula. The yolk weight was next obtained; the albumen, kept meantime in a weighed and covered weighing bottle, was weighed on analytical balances. The albumen was dried in an oven at 105° and placed in a desiccator until used. From a comparison of the dry weight with the original weight the per cent of solids was determined. A sample for analysis consisted of approximately 0.5 gram of the combined *air dry* albumens from the two eggs of a clutch or pair. When no second egg of the clutch was laid a single egg was used alone.

The determination of the total nitrogen was made by the Kjeldahl-Gunning method and the distillate titrated against N/2 NaOH. From the total net weight of the albumen the actual weight in grams of the solids of the albumen was determined; and from this latter figure the weight in grams of nitrogen contained in each albumen was calculated. Although two weighed samples were usually combined to make one Kjeldahl sample, the percentage nitrogen determination thus obtained was applied *separately* to each of the two weighed samples, in order to have separate figures for the *absolute* weight of nitrogen of each individual egg. There is, of course, the possibility that the utilized portion of the combined samples did not consist of equal amounts of the two albumens, and that hence the figure for percentage nitrogen obtained was not equally typical of both samples. But if the admixture and manipulation is thorough and accurate this possibility is surely remote.

PRESENTATION OF DATA

The most important results can be found in condensed form in table 1. If the gross amounts of albumens of "before" and "during dosage" periods be compared it will be seen that this amount is diminished in

can be done is to make weighings on *all* eggs immediately after laying. When the preparation of the sample is delayed after weighing the following inaccuracies develop: The total weight of the egg is too small (0.005 to 0.003 gm. per hour); the total albumen is too small by the amount of the moisture lost to air and to yolk; the yolk is too large by the amount of moisture absorbed from the albumen.

³ With four exceptions the eggs were examined within 5 minutes to 3 hours of laying. These four exceptional eggs were laid long after the usual time and hence were overlooked for a considerable number of hours. Three of these four eggs were from ♀ E97, whose exceptional record will be noted later.

five of the seven groups compared. In two groups (K459 and E97) it is increased.⁴ In all of the seven groups the percent of water is increased during dosage. The percentage nitrogen per gram solids shows considerable fluctuations for these two periods. The amount of nitrogen in grams is decreased in five and increased in two (A347 and E97) of the "during" dosage periods.

Table 2 shows that the average amount of albumen in eggs (of five birds) from the "before" dosage period was 5.5924 gm.; for the "during dosage" period 5.4685 gm. The average percentage of solids was 10.81 in the earlier period and 9.83 in the "during dosage" period. The average amount of nitrogen was 0.0725 gm. per albumen for the "before" dosage period and 0.0661 for the "during dosage" period. These figures all exclude the record of two (E97 and 962) of the seven females.⁵

The amount and composition of the albumen produced after discontinuance of dosage, by birds which had been earlier subjected to prolonged quinine dosage, may next be considered. This "after dosage" period has been divided into three parts, as was done by Riddle and Anderson. Table 1 shows the result for the six individual birds producing such eggs; table 2 presents a summary for five of these. This summary indicates that the percentage nitrogen per gram solids is practically normal for the "after dosage" period as a whole. The percentage of solids, however, is markedly lower than before dosage. The actual amount of nitrogen per albumen is considerably decreased in the whole of the "after dosage" period although the total weight of albumen is only slightly decreased. In fact, in the "later" period the average weight for the individual albumen is slightly increased over the "before dosage" period (table 2).

The fact last mentioned above requires a further statement. In this "later" period the individual albumens are slightly heavier (solids are decreased) than in the control, or pre-dosing period, in spite of the fact that they were accompanied by smaller yolks (see table 1). The control yolks have an average (weighted) value of 1.900 grams, while those of the "later" period average only 1.841 grams. This confirms the view of Riddle and Anderson (p. 96) that there occurs "an excessive

⁴ In both of these cases it will be seen that the whole egg weights of these control (or "before" dosing) eggs were abnormally small as compared with the control eggs produced by the other birds.

⁵ The relative order of none of the above figures would be changed by including the record of these two females. The reasons for excluding the records of these females from table 2 will be given later.

TABLE 1
Principal figures obtained from a study of the production of egg albumen, and of the percentage of nitrogen and water in the albumen, of seven ring-bands dosed with quinine sulfate

NUMBER OF BIRD	DURATION OF DOSAGE	PERIODS AS RELATED TO DOSAGE	NUMBER OF EGGS	AVERAGE WEIGHT		AVERAGE		NUMBER OF NITROGEN TESTS	AVERAGE	
				Eggs	Yolks	Albumens (weight)	Per cent water		Per cent N ₂ per gram solids	N ₂ in grams
152	March 9 to May 21	Before	14	8.578	1.805	5.7011	89.83	7	11.33	0.0654
		During	18	7.956	1.649	5.4171	90.73	9	12.29	0.0616
		First after	2	8.134	1.540	5.4999	90.80	1	12.46	0.0619
		Later	4	8.319	1.678	5.6473	90.89	2	12.44	0.0637
A347	March 24 to May 19	Last	4	8.731	1.829	5.4304	90.93	2	12.47	0.0608
		Before	12	8.070	1.845	5.2167	89.47	7	11.94	0.0639
		During	10	7.706	1.849	5.0344†	90.97†	6	13.22	0.0593†
		First after	2	7.966	1.702	5.2186	91.16	1	11.49	0.0527
K459	March 11 to May 16	Later	4	8.094	1.827	5.1819	90.72	2	12.08	0.0579
		Last	5	7.886	1.867	5.3655	90.31	2	12.63	0.0641
		Before	6	7.557	1.671	5.1862	89.95	4	13.40	0.0701
		During	16	7.784	1.714	5.3267	90.32	8	11.97	0.0620
E106	March 8 to May 18	First after	2	7.528	1.556	5.2364	90.46	1	(16.99)	(0.0845)
		Later	4	8.194	1.795	5.6061	89.13	2	10.99	0.0675
		Last	4	8.197	1.762	5.5012	90.39	2	11.93	0.0633
		Before	9	8.634	1.782	5.9673	88.06	5	11.59	0.0791
		During	16	8.417	1.733	5.8560	89.44	9	12.20	0.0748
		First after	2	8.612	1.657	5.9756	90.48	1	12.42	0.0712
		Later	3	8.783	1.822	6.0326	90.56	2	12.11	0.0693
		Last	5	8.527	1.754	5.7606	90.43	3	12.07	0.0666

E97	March 16 to May 23	Before	8	7 914	1 753	5 2361	89 51	3 8	4	11 67	0 0641
		During	16	8 088	1 715	5 5054	89 37	1 6	9	11 86	0 0696
		First after	2	8 110	1 693	5 6030	90 15	0 8	1	12 10	0 0667
		Later	4	7 495	1 561	5 0882	89 62	7 1	4	12 11	0 0636
		Last	4	7 557	1 595	5 2251	90 37	1 1	2	11 42	0 0574
903	March 8 to May 17	Before	12	8 953	2 269	5 7633	88 61	1 0	7	12 65	0 0858
		During	12	8 536	2 056	5 5745	89 40	1 4	6	12 54	0 0724
		First after	2	8 815	2 041	5 4901	88 77	0 3	1	11 94	0 0721
		Later	3	8 744	2 160	5 7107	90 15	0 4	2	12 13	0 0679
902	March 6 to May 24	Before	16	9 153	1 877	6 1844	89 62	1 0	8	11 85	0 0768
		During	14	8 396	1 645	5 8618	89 76	1 1	7	12 39	0 0703

* The average time interval between laying of egg and preparation of the albumen.

† For only 9 albumens.

or supernormal production of egg albumen . . . in this post-treatment period." These data (table 1) for "first after" periods also, in the main, support their conclusion. In the series of "last" eggs examined here, however, it seems that such influence has quite disappeared.

In any general consideration of the question of altered quantities of albumen per egg, in both the "during dosage" and "after dosage" periods, it must be borne in mind that the size of the egg-yolks—which is normally an effective part of the stimulus⁶ to the secretion of the egg

TABLE 2

Comparative summary of percentage nitrogen and amounts of solids and albumen (weighted averages for all birds exclusive of females 97 and 962)

AVERAGE	BEFORE DOSAGE	DURING DOSAGE	AFTER DOSAGE		
			First	Later	Last
Per cent N ₂ per gram solids.....	12.04	12.37	(13.06)	11.93	12.28
Per cent solids.....	10.81	9.83	9.67	9.72	9.50
Hours before weighing.....	1.08	1.04	0.71	1.01	1.13
Weight albumen in grams.....	5.5924	5.4737	5.5067	5.6095	5.5198†
Weight N ₂ in grams { Expected*.....	0.0725	0.0706	0.0713	0.0727	0.0715‡
Obtained†.....	0.0725	0.0661	(0.0684)	0.0648	0.0638

* Amount of N₂ "expected" from the actually obtained amount of albumen; the figures given presume that the percent of solids, and percent N₂ per gram solids remain as in the period before dosage.

† These figures are weighted averages of amounts actually obtained. They do not check absolutely with calculations from the figures of rows one, two and four; this is because the high and low individual determinations of percentage N₂ and solids do not necessarily coincide with high and low absolute amounts of albumen.

‡ Applies to four birds. One of the five produced no eggs for this group.

albumen—is reduced in both of these periods. In the "during dosage" period the average (weighted) size of the yolks was only 1.788 grams (with egg size of 8.091 grams, and albumens of 5.4737 grams), while for the pre-dosing period these yolks weighed 1.900 grams (with egg size of 8.442 grams and albumens of 5.5924 grams. See third row of figures from bottom of table 2). The average difference in amount of albumen for these two periods is only 0.1187 gram; the average yolk size difference being 0.1200 gram. This would seem to indicate that the change in yolk size does account for the diminished albumen. It

⁶ For discussion see (2, p. 99).

will be shown below that the "weighted averages" from which the above figures are derived fail to show the real situation. Unquestionably the size of the yolk is diminished as a result of the dosage with quinine as is shown for most of the birds of the present series and by all of those observed by Riddle and Anderson.

Since it can be questioned whether, on the basis of the figures given above, the diminished quantity of egg albumen secreted both during and after quinine is not wholly accounted for by the effect of the quinine in reducing yolk size the data of table 1 may be further consulted. For each bird studied it can there be clearly seen that the yolk size produced under quinine is associated with decidedly *smaller eggs* than are yolks of the same or similar size of the "before dosage" or "after dosage" periods. These decidedly smaller eggs must therefore signify smaller albumens for it is not possible to account for the difference as increase in shell under quinine. The data and conclusions of Riddle and Anderson on this matter are also in full accord with this conclusion: The same fact is further shown in the present data by a comparison of the "first after" and "during" periods. In all of these six possible comparisons the yolks were smaller in the "first after" period; nevertheless in four⁷ of these "first after" periods the amount of albumen produced was greater than that of the "during dosage" period. Table 3 may be similarly consulted with like result. It thus becomes nearly certain that the amount of crude albumen or egg-white produced under quinine is less than the normal amount for the size of yolks then being produced and that this reduction is therefore directly due to the quinine.

We may next consider a further modification of the albumen which is certainly produced by the quinine. This concerns the smaller percentage of solids, and correspondingly larger amounts of water, present in albumen produced under dosage with quinine. The albumen of the "before dosage" eggs has 10.81 per cent solids; the "during dosage" 9.83 per cent (table 2). This means that the solids are reduced under the drug by 9.1 per cent of their normal value. This reduction continues moreover into the "after dosage" period for a number of weeks. v. Noorden (1) noted that the diminished excretion of nitrogen in the urine of mammals lasted a period of days after discontinuance of dosage.

We have already noted that the total nitrogen recovered from the "during dosage" period is clearly below that of the normal. We may

⁷ If proper allowance be made for ratio of albumen to yolk (roughly 2:1) five of the six show the above situation.

now observe (last row, table 2) that this reduction of amount of nitrogen is continued through the "after dosage" period. Further, the differences between the "observed" and "expected" amounts of nitrogen are so large as to be clearly inexplicable as indirect results of smaller associated yolks. Here again an effect of the quinine on the nitrogen of the albumen seems unquestionable. Under quinine dosage the egg-albumen of the ring-dove receives more water and less solids than normally; and though these solids probably contain normal or slightly increased percentages of nitrogen, the absolute amounts of nitrogen in these albumens is reduced.

In table 3 is given the detailed record of data as obtained for one of the females. The record is essentially typical and it is not considered necessary to give similar individual records for the other females studied. From the data of this table the effects of the double-dosage of quinine may be observed in the six eggs laid on and after May 4. Calculation will show that during this double-dosage the average size of egg, yolk, albumen, percentage nitrogen per gram solids, and total nitrogen in grams, were all still further reduced beyond the point obtained from the lighter dosage. The figure for moisture, however, is here also slightly reduced. All other birds (including E97 and 962) with the exception of E106 gave essentially similar results for the effect of double-dosage. For the entire group of birds the percentage of water is further decreased in three and increased in four cases.

The condensed record obtained for female E97 has been given in table 1. The reasons for excluding her record from the general summary of table 2 may now be stated. The egg yolks of the "before dosing" period, and of the "later" and "last" periods (table 1) were found at the end of the present experiments to be so much below her previous record (see Riddle and Anderson, (2), table 2) as to cause much doubt as to the normality of this bird. Instead of the normal increase of yolk size which accompanies age (4, p. 391) these yolks had *decreased* in size by 12.8 per cent. Moreover the yolks of E97 failed most pronouncedly to increase in size in "after dosage" periods. Two other birds of this series showed slighter decreases in yolk size (962, decreased by 5.3 per cent; and E106, by 5.2 per cent) at the beginning and end of the present study as compared with their earlier records. These three birds were therefore all killed (September 1) about 50 days after the termination of the records here given in order to see whether *disease* was present and whether this could be responsible for the abnormal size of yolks. In view of the previously noted relations borne

TABLE 3
Details of record of female no. 152

PERIODS AS RELATED TO DOSAGE	DATE OF EGG	EGG WEIGHT	YOLK WEIGHT	WET WEIGHT AL- BUMEN	HOURS BEFORE WEIGH- ING	PER CENT N ₂ PER GRAM SOLIDS	PER CENT WATER	N ₂ IN GRAMS
Before.....	12/ 6	8.043	1.613	5.3417	0.5	8.65	90.30	0.0448
	12/ 8	8.823	1.925	5.5832	2.0		87.20	0.0618
	12/29	8.472	1.793	5.0380	1.0	12.71	94.20	0.0371
	12/31	8.648	1.775	5.5375	1.5		87.70	0.0865
	1/10	8.272	1.705	5.4336	0.5	10.03	90.54	0.0529
	1/12	9.150	(2.025)	6.3886	1.5		(84.80)	0.0973
	1/21	7.943	1.603	5.1951	1.0	10.18	90.15	0.0521
	1/23	9.237	2.088	6.2299	1.5		89.10	0.0691
	2/14	8.128	1.662	5.4884	1.0	12.02	91.15	0.0583
	2/16	8.457	1.688	5.7508	1.3		89.74	0.0709
	2/23	8.253	1.725	5.6818	1.0	12.78	90.25	0.0707
	2/25	9.168	2.060	6.0779	1.5		90.60	0.0730
	3/ 4	8.377	1.673	5.6671	1.0	12.95	90.87	0.0670
	3/ 6	9.123	1.940	6.4012	1.0		91.03	0.0743
	Average	8.578	1.805	5.7011	1.2	11.33	89.83	0.0654
During.....	3/14	7.370	1.690	4.8552	0.5	12.52	90.65	0.0568
	3/16	7.787	1.772	5.1732	1.0		91.61	0.0543
	3/23	8.023	1.598	5.6258	0.5	13.04	90.55	0.0762
	3/25	8.477	1.885	5.7945	2.0		92.99	0.0529
	4/ 2	7.672	1.465	5.4720	2.0	12.52	90.56	0.0646
	4/ 4	8.733	1.880	6.1000	1.0		90.40	0.0733
	4/10	7.382	1.523	5.0040	1.0	13.03	90.88	0.0594
	4/12	8.390	1.700	5.6841	1.3		91.71	0.0613
	4/18	7.945	1.605	5.5669	0.0	12.29	90.29	0.0664
	4/20	8.567	1.745	5.9530	0.0		90.98	0.0659
	4/26	7.700	1.550	5.3824	0.0	12.26	90.18	0.0647
	4/28	8.605	1.778	5.4753	0.0		90.52	0.0636
	5/ 4	7.748	1.620	5.2142	0.5	12.00	90.34	0.0604
	5/ 6	7.883	1.562	4.7318	0.3		90.93	0.0514
	5/13	7.623	1.600	5.0609	0.5	11.70	90.35	0.0571
	5/15	7.955	1.640	5.5880	0.5		87.42	0.0702
	5/21	7.478*	1.488	5.3010	1.0	11.30	90.60	0.0562
	5/23	7.870*	1.592	5.5271	1.3		91.24	0.0547
	Average	7.956	1.619	5.4171	0.7	12.29	90.73	0.0616
First after.....	5/29	7.790	1.380	5.0711	1.0	12.46	90.90	0.0574
	5/31	8.478	1.700	5.9287	0.0		90.70	0.0664
	Average	8.134	1.540	5.4999	0.5	12.46	90.80	0.0619

TABLE 3—Continued

PERIODS AS RELATED TO DOSAGE	DATE OF EGG	EGG WEIGHT	YOLK WEIGHT	WET WEIGHT AL-BUMEN	HOURS BEFORE WEIGHING	PER CENT N ₂ PER GRAM SOLIDS	PER CENT WATER	N ₂ IN GRAMS
Later.....	6/6	7.843	1.535	4.6925	0.0	11.97	90.39	0.0539
	6/8	8.443	1.700	5.9637	0.0		90.87	0.0651
	6/14	8.330	1.638	5.8578	0.0	12.91	90.88	0.0689
	6/16	8.780	1.842	6.0752	1.0		91.44	0.0671
	Average	8.349	1.678	5.6473	0.3	12.44	90.89	0.0637
Last.....	6/23	8.448	1.775	4.3691	1.3	12.52	89.84	0.0556
	6/25	9.153	1.997	5.7623	1.3		91.57	0.0608
	7/1	8.500	1.675	5.5453	1.5	12.42	91.08	0.0614
	7/3	8.823	1.872	6.0449	1.5		91.26	0.0656
	Average	8.731	1.829	5.4304	1.8	12.47	90.93	0.0608

* Dosage of quinine doubled during this period.

by yolk size to the total amount of albumen this point is of considerable importance. The result of the post-mortem examinations of these three birds is given herewith:

♀ E97. Killed (September 1) for autopsy. Spleen much enlarged; with several firm tubercles throughout. Liver somewhat enlarged; texture soft. A very large cheesy tubercle in left lobe of liver at upper anterior border where it is also adherent to pericardium. Two tubercles on intestine, hard, apparently non-progressive. Oviduct medium functional. Largest ovum in left ovary about 3.5 mm.; plain detached traces (3 points) of right ovary. Some tuberculosis in left lung; well walled-off, apparently non-progressive. Pancreas and intestines extremely pale. Joints entirely free of tuberculosis. No lice present. Body not at all emaciated. Last egg laid August 12.

♀ 962. Killed for autopsy. This bird, obviously tubercular, had been removed from breeding pen on June 29. Body cavity entirely filled with purulent fluid. Very advanced tuberculosis in liver; this being enlarged, softened, and with numerous cheesy tubercles. Spleen enormously enlarged (about 3 grams). Oviduct small. Largest ovum in left ovary less than 1 mm. A trace of right ovary. Large tubercle in left lung; right lung healthy. Last egg laid May 23.

♀ E106. Healthy, killed for autopsy. Fully functional oviduct; two large ova in left ovary nearly ready to ovulate (9 and 11 mm.), also others nearly 5 mm. A trace of right ovary. Spleen and liver normal. A small single, cheesy, tubercular cyst or nodule at the tip of the right lung. Bird otherwise wholly normal in appearance. Bird had laid two eggs 5 and 3 days (August 28) before autopsy.

These records make it fairly evident that some at least of the abnormally small eggs of E97 were produced by a tubercular bird, and that

this tuberculosis was probably of the slowly progressive type that has been often observed in the birds of this collection. Moreover, as earlier noted, of the four instances in which the weights and preparations of individual samples were long delayed, three of these occurred among the eggs obtained from this bird. Such delays modify the results, and corrections for such delays are difficult and not wholly accurate. For all of the reasons already mentioned the record of E97 is excluded from table 2. The autopsy of female 962 shows a very advanced stage of progressive tuberculosis. Although the egg and yolk weights of this female were not far from normal for the "before dosage" period, her failure to produce any eggs in the "after dosage" period affords reason for excluding the data obtained from her, as has been done in table 2. The autopsy of E106—the general size of whose eggs was least abnormal throughout—shows on the other hand that this bird was practically or almost entirely unaffected and gives no warrant for the exclusion in table 2 of the data obtained from her.

Two further topics remain to be mentioned. There seems to be no report in the literature of any nitrogen determinations on doves' eggs other than those here reported. Pennington (5) has made nitrogen determinations on the egg albumen of two varieties of domestic fowl. The eggs for these determinations were collected under very nearly ideal conditions. With six to eleven determinations, each based on six to eighteen eggs, the nitrogen of the albumen (water-free) averages 14.28 per cent for Plymouth Rocks and 14.63 for Leghorns. The individual determinations ranged from 13.20 to 15.75 in the one case, and from 14.01 to 14.96 in the other. Our figures show averages varying around 12.00 per cent. The averages for the different periods among the several birds vary from 11.33 to 13.24, although in the individual records there are some wide exceptions. Some wide exceptions are also to be found among the individual determinations of amount of solids.

For the purposes of such a summary presentation as has been made, in table 2 particularly, our data would be more nearly ideal if equal numbers of eggs might have been obtained from each of the birds for each period. But from whatever standpoint the data are examined it seems clear that the nitrogen output of the albumen-secreting gland of ring-doves is diminished under quinine.

CONCLUSIONS

Fresh-laid dove eggs contain about 12 per cent nitrogen per gram of solids.

The data of Riddle and Anderson on the reduction of egg size and yolk size under quinine treatment are further corroborated by the records of six of seven birds retested: Egg size and yolk size are decreased during dosage and increased after dosage is discontinued.

The normal quantity of (a more dilute) albumen is restored quickly after discontinuance of dosage.

Less albumen is produced during dosage than before. Relatively more (of a more dilute) albumen is produced after dosage is discontinued than during dosage.

The loss of weight or amount of albumen under quinine consists in *a*, a loss of total substance; and *b*, a disproportionate loss of solids.

The loss of solids is accompanied by a loss of nitrogen. When the amount of albumen is later increased, in the after-dosage period, the nitrogen does not increase in full proportion. The percentage of water remains high in albumen produced in these after-dosage periods.

It seems clear that dosage of ring-doves with quinine sulfate causes less than the normal amount of nitrogen to be released by the albumen-secreting gland of the oviduct during the secretion of egg-albumen.

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THE NOSE-LICKING REFLEX AND ITS INHIBITION

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The chief and obvious purpose of the licking of the nose in animals is to clean its orifices. To accomplish that end the anterior part of the tongue must be freely movable and long, and the space which separates the nose from the mouth must be comparatively short. In animals in which these conditions are present, in dogs for instance, nose-licking is not merely an incidental phenomenon; it is a steady and apparently indispensable companion of the act of drinking, while the nasal orifices are mostly under the surface of the liquid. Furthermore, dogs get the liquid into their mouth not by the mechanism of suction, like in man, but by giving the anterior part of the tongue a spoonlike formation and throwing the liquid into the posterior oral cavity. Under these circumstances it certainly frequently occurs that some of the liquid is thrown into the nasal openings. These conditions obviously interfere with the respiration, and it is apparently a necessity for the animal, in order to facilitate its breathing, to frequently interrupt the drinking and cleanse the openings of the nose by means of licking.

The licking is accomplished by successive coördinated contractions of various voluntary muscles of the anterior part of the tongue which are under the control of the hypoglossus nerves. The entire procedure of the nose-licking makes the impression of being a conscious, voluntary act. Furthermore, the licking movements do not appear when the animal is under the influence of ether or chloroform anesthesia.

As far as we know, the physiological literature contains no indication that these movements may also be of a reflex nature. At the last meeting of the American Physiological Society we reported briefly on a mechanical method of anesthesia (this Journal, 1919, xlix, 120). The method consists in a carefully applied indirect concussion of the skull over the parietal bones. This procedure, when properly per-

formed, abolishes voluntary motions and all sensory reactions, without affecting the reflexes. For instance, strong pinching of the skin or strong electric stimulations of it or of exposed sensory nerve trunks (supra-orbital or lingual), leaves the animal perfectly quiet and without any evidence that it feels any pain. The reflexes, however, are very little affected, if any. The respiratory and vasomotor centers remain apparently intact; respiration continues in a normal rhythm, and the blood pressure remains unaffected; also the reflexes of these centers are unimpaired, for instance, stimulation of the central end of the vagus nerve causes inhibition of the respiration, and stimulation of the central end of the sciatic nerve causes an unmistakable rise of blood pressure; the eyelid and corneal reflexes appear to react in a normal fashion.

This signifies that in the indirect concussion of the brain, when properly performed, we possess a method which is capable of completely abolishing voluntary motions and sensations without perceptibly interfering with reflex actions. Employing this method, we tested the nature of the nose-licking act. The results which were obtained were constant; they are twofold and are very instructive.

We shall first mention the fact that *compressing in some way, for instance, by hemostatic forceps, the tip end of the nose or of the anterior part of the septum, causes a very characteristic nose-licking.* The appearance of this seemingly normal nose-licking movement in an animal which shows no other reaction to a pain-producing stimulus is a surprising sight. The nose-licking movements in such an animal are evidently of reflex origin, a fact which agrees with the previously mentioned observation that reflexes are not abolished under this method of mechanical anesthesia.

The second noteworthy observation is the fact that the nose-licking reflex occurs only after the cessation of the adequate stimulus. *During the pressure no attempt of nose-licking is made, may the pressure be ever so strong.* It seems to us that these observations express the facts that *during the stimulation the nose-licking reflex is inhibited* and that it may make its appearance only after the discontinuation of the stimulus. These phenomena were obtainable for many hours, that is, as long as the animal was under observation.

In other words, our experiments brought out the instructive facts *that the phenomenon of nose licking is or may be a purely reflex act, and that this reflex mechanism consists of two parts: an inhibition of nose-licking during stimulation, and the setting in of the nose-licking movements soon after the discontinuation of the pressure stimulus.*

Obviously the afferent path of this reflex is located in the ophthalmic branch of the trifacial nerve, and the nerve fibers of the hypoglossus which convey the motor impulses to the anterior part of the tongue contain the efferent nerve fibers of this coördinated reflex. No doubt there is room for a further study of many details of this new reflex, and the mechanism may have to be considered later from various angles. There is, however, one point of view which we wish to discuss here.

It seems to us that our observations on the nose-licking reflex—namely, that it appears only after discontinuation of the compression of the tip end of the nose or the septum and that during this compression the reflex is inhibited—can be explained best by the following assumptions. First, the afferent path of this reflex consists of two antagonistic nerve fibers, nerves, the stimulation of which causes an impulse for the excitation of the muscles performing nose-licking; and nerve fibers, the stimulation of which causes an inhibition of the motor part of this reflex. Second, that when both kinds of the reflex fibers are stimulated simultaneously, the response of the reflex inhibitory fibers predominates to such a degree as to completely obscure the presence of the impulse of the reflex excitation. Third, that the response of the reflex inhibitory fibers to the stimulation possesses either a very weak after-effect, or none at all, while the stimulation of the reflex exciting fibers continues its effect after cessation of the stimulation, to such an efficient degree as to bring out the nose-licking reflex in a definite fashion. In other words, we interpret our phenomenon by assuming that when both (antagonistic) nerve fibers are stimulated simultaneously by compression, the effect on the inhibitory fibers predominates during stimulation; but the nose-licking reflex makes its appearance after the discontinuation of the stimulation by virtue of the efficient after-effect of the reflex excitation impulses.

The foregoing several assumptions are sufficiently supported by facts well known in the physiology of the nervous system. For instance, the assumption that a simultaneous stimulation of antagonistic nerves may bring out the effect of the inhibitory impulses during stimulation while the exciting action may outlast the stimulation and appear after its cessation, in consequence of the after-effect of the exciting impulse, is well illustrated by the relations of the vagus and accelerans nerves in their action upon the heart. As is well known, stimulation of the peripheral end of the vagus causes inhibition, while stimulation of the accelerans nerve causes an acceleration and augmentation of the heart

beats. Now when both nerves are stimulated simultaneously, and the stimulus is also discontinued simultaneously, the heart stops beating during stimulation, while after discontinuing the stimulus, the heart beats more frequently and strongly than before the stimulation. This is due to the experimentally well-established facts that the inhibitory response of the vagus nerves predominates during stimulation and that after cessation of the stimulus a long after-effect of the accelerating nerves comes to the fore. In other words, we have here a well-established instance of results of simultaneous stimulation of two antagonistic nerves in which the inhibitory impulse responds during stimulation and the response of the exciting nerves appears after cessation of the stimulus due to an after-effect of the latter type of nerves. However, it must be borne in mind that in this instance the mentioned characteristic results take place in the periphery, within the heart, and not, as is the case in the nose-licking reflex, within a center located in the central nervous system.

On the other hand, the assumption that a single mechanical stimulus may cause simultaneously inhibitory and exciting reflexes in the spinal cord is illustrated by the facts discovered by Sherrington, namely, that a mechanical stimulus of a flexor muscle may cause simultaneously an excitation of the flexor and an inhibition of the extensor muscles (and *vice versa*)—Sherrington's "reciprocal innervation." But here again this instance differs from our observation on the nose-licking reflex, in that the stimulation of both antagonistic nerve fibers causes effects only during stimulation and not after its cessation, and that the effects of the stimulation become manifest in different groups of muscles; while in the nose-licking reflex, the effect of simultaneous stimulation of the antagonistic nerves becomes manifest in one and the same muscle group, and further, at different times, the exciting reflex effect appearing after the cessation of the stimulus, while the inhibitory reflex effect is active during stimulation.

Another illustrating fact is to be found in the observations of Kroecker and Meltzer on the propagation of the peristaltic wave within the esophagus. Throughout the entire length of the gullet the inhibitory action runs ahead of the action which causes the successive contractions of that organ. But it must be pointed out that in the deglutition mechanism the mentioned phenomenon becomes manifest in muscle fibers which are not under the control of volition; we have no definite knowledge as to the rôle which inhibition may play in the buccopharyngeal part of the mechanism of deglutition.

We may perhaps also refer here to the mechanism of the "self-regulation" of respiration. According to Herring and Breuer, distention of the lung causes an inhibition of the inspiratory and an excitation of the expiratory muscles, while collapse of the lung causes an inhibition of the expiratory and an excitation of the inspiratory muscles. In this theory it is assumed that the collapse of the lung is a stimulus and a specific one for the expiration; in other words, distention and collapse are different stimuli; each stimulus acting separately and specifically on the two antagonistic parts of the respiratory mechanism. Meltzer suggested (Du Bois-Reymond's *Arch. f. Physiol.*, 1892, 340) that in the mechanism of "self-regulation" there is only one stimulus for both antagonistic parts of the respiratory function; it is the distention of the lung which stimulates simultaneously both sets of antagonistic nerves; but both sets of nerve fibers differ in their response to the same stimulus by two characteristics, namely, the responses of the inspiratory fibers *a*, predominate during the stimulation (distention) and *b*, possess very little or no after-effect; while the impulses in the nerve fibers which control the expiratory mechanism are obscured during the stimulation but possess a long and efficient after-effect which becomes manifest after the discontinuation of the stimulus (distention). In other words, the inspiration is due to the predominating response to the stimulation of the inspiratory nerves during the distention, and the expiration is due to the after-effect of the impulses carried by the expiratory nerves which are dormant during the distention. According to this theory of respiration, the elements of the reflex mechanism for the function of respiration are to a great degree similar to those which we have assumed as underlying the nose-licking reflex. In the mechanisms of both reflexes the mechanical stimulus affects two antagonistic sets of nerve fibers simultaneously, but the effect of stimulation of one set of fibers predominates during stimulation and the stimulation carries no after-effect; while the impulses of the antagonistic nerves are dormant during stimulation, but become manifest after discontinuation of the stimulation on account of the long and efficient after-effect.

We believe that the element of the after-effect of stimulation is an important factor in the mechanisms of many functions. However, experimental physiology has hitherto completely neglected the study of the rôle which the after-effects of stimulations may actually play in the functions of the animal body.

SUMMARY

Indirect concussion of the brain may abolish voluntary movements and the sensation of pain, without affecting reflexes. Indirect concussion, when properly carried out, may offer a useful method for bringing out the presence of new reflexes, especially those of the brain.

Nose-licking, at least in dogs, is a reflex act, the motor part of which, however, may, as in many other reflexes, also be performed voluntarily.

In an animal under mechanical anesthesia, induced successfully by indirect concussion of the brain, a nose-licking reflex may readily be brought about by compression of the tip end of the nose or the anterior part of the septum. This reflex is characteristic in that it appears only *after* the discontinuation of compression; it does not appear *during* the compression.

This characteristic behavior is explained by the assumption that the compression stimulates simultaneously two antagonistic sets of nerve fibers, reflex exciting and reflex inhibitory nerves. The influence of the impulse of the reflex inhibitory fibers predominates during the stimulation (compression); the impulses carried by the reflex exciting fibers are dormant during the stimulation but become manifest after discontinuation of the stimulus by virtue of the long and efficient after-effect of this set of nerve fibers.

INFRA-RED RADIANT ENERGY AND THE EYE

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A number of years ago speculation was rife regarding the possibility that the absorption of infra-red radiant energy by the eye-media resulted in eye-fatigue. In fact, statements were made by eminent men that irritation and fatigue in the eye were due largely to this thermic effect. These statements were widely quoted with the result that many have accepted this explanation of the source of irritation and fatigue of the eyes under artificial illumination. Although the assumption may be proved eventually to be true, the author is unaware of any definite experimental foundation at the present time. Without declaring for or against this assumption, the author, several years ago, computed the amounts of energy absorbed in the eye-media under various conditions of illumination and also the energy-densities throughout the optical path in the eye. As a consequence two papers (1), (2) were published where they would reach those interested in lighting.

More recently there has developed quite extensively an opinion that eye-glasses, especially in the industries, should not transmit infra-red radiation. Therefore, it appears worth while to present some of these data within convenient reach of the physiologist and ophthalmologist who doubtless are best fitted to supply experimental evidence regarding the possibility of infra-red radiation causing visual discomfort, eye-fatigue or permanent injury to the eye-media. At present infra-red radiation stands convicted purely upon circumstantial evidence, and although it is not the intention to present a brief for or against this radiation, it appears desirable to show the type of data upon which the conviction is based.

Crookes (3) inferred "that it is to the heat rays rather than to the ultraviolet rays that glass-workers' cataract is to be ascribed" because these rays (ultra-red) are "present in the radiation from molten glass in far greater abundance than the ultraviolet rays." A number of questions of fundamental importance immediately arise. First, and of

primary interest, is the question of the existence of glass-blowers' cataract. The author has not encountered any qualified individuals in the glass industry who admit that cataract is prevalent among glass-blowers. Furthermore, even though such prevalence be admitted for the sake of analysis, there is still the possibility that the causes when traced to their source may lead the investigator far from the molten glass into other conditions of working or living (4). Infra-red radiation may be found to be effective in causing cataract but possibly only in conjunction with some other agency or condition. In fact, it may be completely exonerated in the case of glass-workers because ultraviolet radiation is emitted by molten glass as Crookes himself determined. Spectrograms made by him on photographic plates extended into the ultraviolet as far as 0.3345μ when the exposure was prolonged sufficiently, but because of the low intensity of ultraviolet radiation compared with that of infra-red radiation, Crookes inferred that the blame must be attached to the latter. This is unphilosophical even when viewing the situation superficially and is extremely so when considering the chemical activity of ultraviolet radiation with the comparative ineffectiveness of infra-red radiation in this respect.

The properties of radiant energy are not well defined as to wave-length. For example, the chemical effect of ultraviolet radiation varies with the wave-length and this variation varies with the chemical process. Furthermore, it is misleading, for example, to state that ultraviolet radiation is chemically active; that visible radiation arouses the sensation of luminosity; and that infra-red radiation is "heat" energy. Either directly or indirectly these various radiations have many properties in common. When measured as heat energy, radiations of all wave lengths are alike,—that is, they are readily converted into heat energy by absorption. A statement that infra-red radiation is the cause of cataract or eye-fatigue carries with it the possibility of condemnation of visible radiation on the same score because of certain similarities of the two radiations.

As shown later, if infra-red radiation is detrimental owing to its heating effect under conditions which do not "burn" the skin or eye-membranes, then sunlight, owing to its enormous intensity, must be looked upon with suspicion. Even the visible radiation in sunlight is quantitatively large owing to the extreme intensity, and if the thermic effect of radiation is harmful, then sunlight is dangerous even when the water-vapor of the atmosphere has absorbed all the infra-red radiation.

Perhaps one of the reasons for the growing belief that infra-red radiation is harmful to the eyes may be found in attributing to this energy a destructive ability similar or analogous to that of ultraviolet energy. But such a property is not established for infra-red. In fact, it appears to be even less destructive to animal tissue than some of the visible radiation.

Notwithstanding this line of reasoning and the lack of direct experimental evidence, infra-red radiation has been condemned so often that many now believe it to be injurious. In fact, this conviction is so seriously accepted in many quarters that it is gaining rapidly and bids fair to be very generally accepted by those interested in eye-protection. This is illustrated for example by a recent technical paper (5) containing excellent data under the title, "Glasses for protecting the eyes from injurious radiations." Although the authors in their introductory remarks call attention to the lack of proof "that infra-red rays have other than a thermic (if any) effect," the data presented largely pertain to infra-red radiation. To the indiscriminating the title of the paper containing, for the most part, data pertaining to the infra-red radiation, carries with it a strong implication if not a complete conviction that infra-red radiation is harmful to the eyes even for intensities too low to "burn" (in the ordinary sense) the skin and eye-media.

When considering vision, the infra-red radiant energy is at least useless and it is well to dispose of it if this can be done without too much expense and without injustice commercially. The brief discussion presented in the foregoing paragraphs does not aim to exonerate infra-red radiation but to focus attention upon the lack of experimental evidence. Many are now capitalizing this (at present) unfounded suspicion and therefore this is an important problem confronting the physiologist.

The data presented in this paper do not directly reach the root of the problem but they are of considerable importance. Energy quantities and densities in the eye-media are established herein and should aid the physiologist who is interested in the question. This paper is confined purely to the physical aspects of spectral energy-distribution in illuminants, of the absorption by the eye-media, of optical laws, of luminous efficiency of illuminants, etc. The radiation from the theoretical "black-body" at various temperatures is considered and industrial processes involving high temperatures may be compared in terms of these data because most bodies emitting radiant energy by virtue of their temperature may be placed at least approximately on the black-body scale. In fact, it is enlightening and not difficult to arrange

industrial processes approximately on a temperature scale according to the approximation of their emitted radiation to that of the theoretical black-body.

Any one familiar with the spectral distribution of energy in the radiation from ordinary light-sources is certain that less energy per lumen is incident upon the eye as the temperature of the radiator is increased, provided that the light is due to purely temperature radiation. The computations in this paper will be confined to purely temperature radiation or radiation from bodies which deviate but little from it. Just what relative amounts of energy are absorbed in the various eye-media and how the amount of absorbed energy varies with the temperature of the source have not been determined, although Vogt (6) has described elaborate experiments which show roughly the transmission of the eye-media in various regions of the spectrum. His results roughly confirm the more refined experiments of Aschkinass (7). Fortunately, Aschkinass has clearly established the transmission of the eye-media throughout a wide spectral range and has obtained other data which enable certain computations to be made. He found that the various eye-media transmitted the visible and infra-red rays in the same manner as like thicknesses of water. The only discrepancies found were for the transmission of the cornea for the visible and "near" infra-red rays. The differences found in that case he attributed to the film which rapidly forms over the dead cornea, rendering it less transparent, for the absorption-bands were well defined and in the same position as for water.

The intensity of radiation after traversing any depth, d , can be computed from the following equation:

$$I' = Ie^{-xd}$$

where I and I' are the original and final intensities respectively, e is the base of Napierian logarithms, and x is the extinction-coefficient. This can be further simplified for purposes of calculation thus

$$\frac{I'}{I} = T = e^{-xd}$$

or

$$\text{Log } T = -xd \log e$$

where T is the transmission-coefficient. If I is taken as unity, of course the value of I' is numerically equal to the transmission factor. Aschkinass gives a table of extinction-coefficients for water for radiant energy of

wave-lengths from 0.45μ to 8.49μ . It is thus possible to compute the transmission of the various eye-media for this range of wave-lengths. Aschkinass did this for the total eye but not for the various media. For the purpose of computation, thicknesses of water corresponding to the various eye-media were taken. These are reproduced in table 1.

TABLE 1

Thicknesses of water corresponding to thicknesses of various eye-media

	<i>Cm. of water</i>
Cornea.....	0.06
Aqueous humor.....	0.34
Crystalline lens.....	0.42
Vitreous humor.....	1.46
Total depth of eye.....	2.28

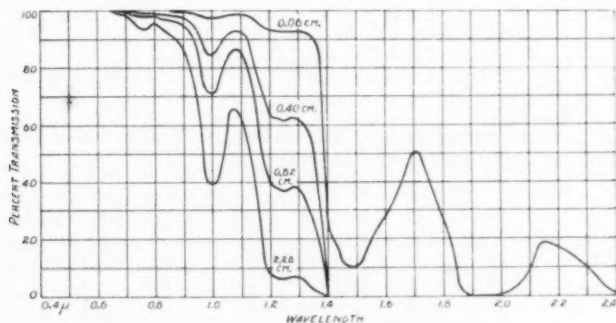


Fig. 1. Transmission of various layers of water corresponding to the eye-media.

Spectral transmission-curves were initially computed for four thicknesses of water, namely, 0.06 cm., 0.4 cm., 0.82 cm. and 2.28 cm. The first thickness corresponded to the cornea, the next to the cornea plus the aqueous humor, and so on. Obviously, the amount of energy absorbed in the aqueous humor, for example, is readily found by obtaining the absorption of the first two thicknesses and taking their difference. This was the general procedure. The spectral transmission curves of the four thicknesses of water are shown in figure 1.

The next point of interest was to apply these transmission-curves to the curves representing the spectral energy-distribution of black-bodies at various temperatures and also to those of various illuminants. This was done by multiplying the ordinates of the spectral energy-curves by

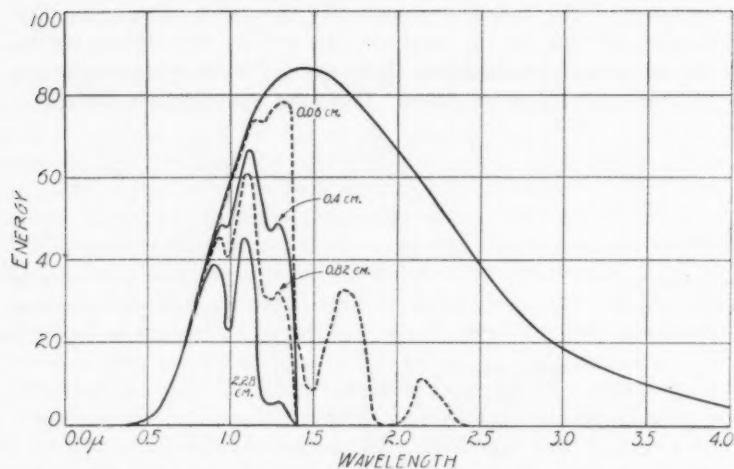


Fig. 2. Spectral transmission of radiant energy from a 4-watt-per-candle carbon lamp through various layers of water.

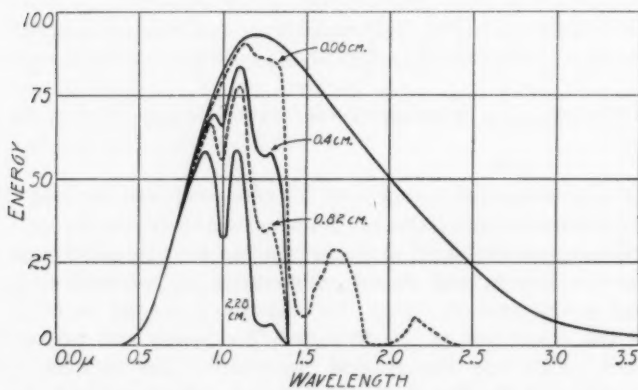


Fig. 3. Spectral transmission of radiant energy from a tungsten lamp (7.9 lumens per watt) through various layers of water.

the corresponding transmission-factors. Figures 2 and 3 show the results of this process with the spectral energy-curves of a 4-watt-per-candle carbon incandescent lamp and that of a 1.25-watt-per-candle tungsten lamp (7.9 lumens per watt) respectively. The numbers on the curves represent the thickness of water. For example, the percentage of total energy radiated from the carbon lamp which is transmitted by the cornea is found by obtaining the ratio of the area under this spectral transmission-curve (0.06 cm.) to the total area under the energy-distribution curve. The difference between this and unity gives the absorption of the cornea. The same process with the curve, 0.4 cm., gives the percentage of energy transmitted by the cornea and aqueous humor.

TABLE 2
Percentage of radiant energy absorbed in the eye-media

SOURCE	PERCENTAGE OF TOTAL ENERGY ABSORBED IN							
	Water of depth				Cornea	Aqueous Humor	Lens	Vitreous Humor
	0.06 cm.	0.4 cm.	0.82 cm.	2.28 cm.				
Black body at 2000° absolute..	68.8	80.6	83.8	89.7	68.8	11.8	3.2	5.9
Black body at 2500° absolute..	51.7	63.3	68.3	76.7	51.7	11.6	5.0	8.4
Black body at 3000° absolute..	38.5	49.8	55.7	65.1	38.5	11.3	5.9	9.4
Black body at 4000° absolute..	22.8	31.7	37.2	45.9	22.8	8.9	5.5	8.7
Black body at 5000° absolute..	13.0	19.6	23.4	30.4	13.0	6.7	3.8	7.0
4-w. p. c. treated carbon lamp.	64.1	77.3	81.0	87.9	64.1	13.2	3.7	6.9
1.25-w. p. c. tungsten lamp....	50.4	64.5	70.5	80.0	50.4	14.1	6.0	9.5

Obviously, the difference between the two transmission-factors gives the percentage of total energy absorbed in the aqueous humor, and so on. These percentages are found in table 2 and plotted in figures 4 and 6 for black-bodies at temperatures ranging from approximately 2000 to 5000 degrees absolute. At temperatures above 5000 degrees, the ultraviolet energy becomes appreciable, so no computations are given for higher temperatures. The curves would rise again for temperatures beyond 5000 degrees absolute. The energy of shorter wave-length than 0.35μ radiated from a black-body at 5000 degrees absolute was found to be 3.8 per cent of the total energy.

Though the eye-media are found to transmit the visible and infra-red rays in the same manner as water, this is not true for ultraviolet radiation. Water is transparent to short-wave radiation far into the extreme ultraviolet. In fact, no noticeable absorption was found for

any of the ultraviolet radiation from the quartz mercury arc. It has been concluded by some that near ultraviolet radiation is chiefly absorbed in the eye-lens owing to the fact that it strongly fluoresces under the influence of these rays. This conclusion has been strongly confirmed by spectro-photographic evidence. However, for black-body temperatures below 5000° absolute the ultraviolet rays need not be considered from the standpoint of the temperature effects due to absorption of this energy. In figure 4 are plotted the percentages of total black-body radiant energy absorbed by the various eye-media. It will be noted

TABLE 3
Absorption of radiant energy in watts per lumen in the eye-media

SOURCE	WATTS PER LUMEN ABSORBED IN							
	Water of depth				Cornea	Aqueous Humor	Lens	Vitreous Humor
	0.06 cm.	0.4 cm.	0.82 cm.	2.28 cm.				
Black body at 2000° absolute.....	0.153	0.179	0.186	0.20	0.153	0.026	0.007	0.013
Black body at 2500° absolute.....	0.04	0.049	0.053	0.061	0.04	0.009	0.004	0.008
Black body at 3000° absolute.....	0.012	0.0156	0.0174	0.0202	0.012	0.0036	0.0018	0.0028
Black body at 4000° absolute.....	0.0035	0.0049	0.0057	0.0071	0.0035	0.0014	0.0008	0.0014
Black body at 5000° absolute.....	0.0015	0.0023	0.0027	0.0035	0.0015	0.0008	0.0004	0.0008
4-w. p. c. treated carbon lamp.....	0.247	0.297	0.312	0.338	0.247	0.05	0.0015	0.026
1.25-w. p. c. tungsten lamp.....	0.064	0.082	0.089	0.101	0.064	0.018	0.007	0.012

that for the cornea these percentages rapidly decrease with increase of temperature of the source, but much less rapidly for the aqueous humor, while the percentages of absorbed energy are a maximum for the lens and vitreous humor at about 3500° absolute. (See table 2). This would hardly be foreseen without computation. It is seen that most of the energy is absorbed in the outer portion of the eye. In reality, this absorption rapidly decreases as the depth of the absorbing layer increases. This, of course, is to be expected from the exponential character of the foregoing equation relating thicknesses of the eye-media with the transmission-factors.

So far only percentages of energy absorbed have been considered. However, it is important to reduce the data to a common basis, that is,

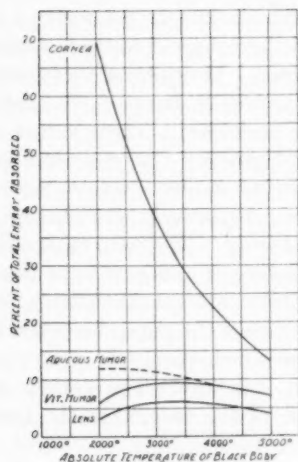


Fig. 4

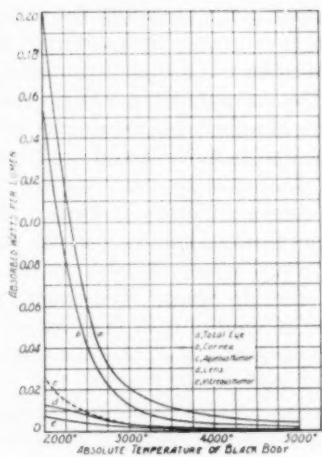


Fig. 5

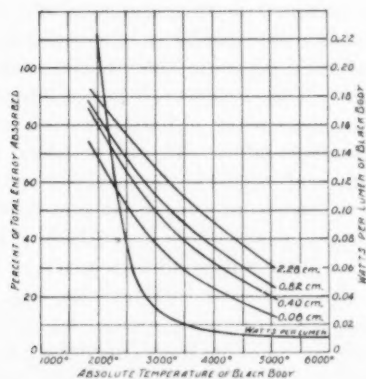


Fig. 6

Figs. 4, 5 and 6. Percentage of total radiant energy absorbed in various eye-media, watts absorbed in eye-media per lumen in usual percentage of light, and percentage of total radiated energy absorbed in various layers of water.

to find the actual watts absorbed per lumen. This was readily done by combining the foregoing percentages with the lumens per watt of the various sources. In figure 6 are plotted the values of watts per lumen for the black-bodies at various temperatures. Multiplying these values by the corresponding values from the curves in figure 4, the actual watts absorbed per lumen are found in each case. These values are presented in table 3 and are plotted in figure 5. Curve *a* represents the absorption by the total eye (2.28 cm. of water); curve *b*, that by the cornea. Curves *c*, *d* and *e* represent, respectively, the absorption by the aqueous humor, lens and vitreous humor. These curves indicate the actual power absorbed in the eye-media per lumen of light flux in the entering beam. The computations take into consideration only a beam of light of such dimensions that it enters the pupil; however, the exterior portions of the eye must absorb much energy in rays which could not possibly enter the pupillary aperture. The cornea and aqueous humor, besides absorbing most of the energy in the useful beam, no doubt absorb a great deal more energy.

It is thus seen that the outer layer of the cornea absorbs a large portion of the energy which is not active in producing the sensation of light, and, as is to be expected, the absorbed energy per lumen of light flux incident upon the retina rapidly decreases with increase of temperature of the source. There would be an increase again for temperatures higher than about 5000° absolute due to the increasing amount of short-wave radiation. This, however, is not of interest here, because a large amount of the short-wave radiation would not be tolerated on account of its destructive effect. It will be noted that about thirty times as much energy is absorbed in the total eye per lumen of tungsten light as per lumen of light from a black-body at 5000° absolute. This same ratio would hold approximately for sunlight if it were not for the moisture in the atmosphere which absorbs much of the infra-red rays before they reach the earth and therefore the eye. This is perhaps fortunate considering the enormously greater intensities of illumination encountered in daylight. For instance, according to F. E. Fowle (8), the amount of precipitable water existing in the form of water-vapor between the top of Mount Wilson and the outer limits of our atmosphere during fair weather from June to November, 1910 and 1911, was found to vary from 0.2 cm. to 2.8 cm. The average quantity present was 0.69 cm.

Another point worthy of consideration is the energy-density at various points in the eye along the optical path. Obviously, owing to

the optical system through which the radiant energy passes, the energy-density varies in different parts of the eye. Where the energy is more concentrated the more serious effects might be expected.

Utilizing the foregoing and some additional data, the transmission of various depths of the eye (measured from the anterior surface of the cornea) is readily obtained.

The spectral transmission-curves for radiation from a black-body at various temperatures and from a carbon and a tungsten lamp are shown in figure 7. Neglecting atmospheric absorption, which will be discussed later, the radiation from the sun can be assumed, for comparison purposes, to be approximately similar to that of a black-body at 5000° absolute.

In order to obtain an idea of the energy-density in various parts of a beam of light passing through the eye, it is necessary to determine the path of the beam. Obviously, the path of the useful beam is slightly different as the eye is accommodated for near or distant vision. Data regarding the refractive indices, thicknesses and curvatures of the various surfaces of the eye-media as

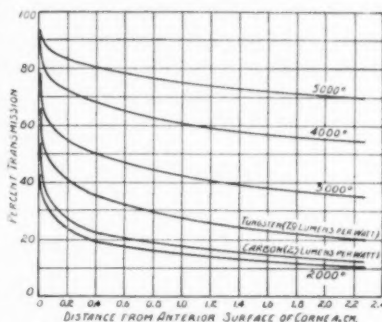


Fig. 7. Transmission of various depths of the eye for the radiation from different sources.

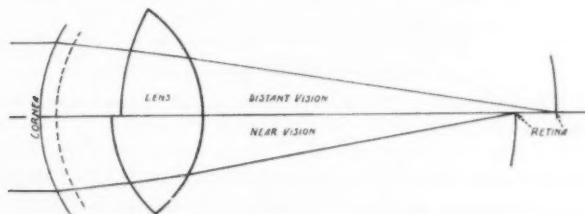


Fig. 8. Path of light in the eye (small object).

determined by Helmholtz were used. Only the beam that enters the pupillary aperture (in this case assumed to be 5.8 mm. in diameter) was considered. Computations give the paths for near and distant vision for a small object as shown in figure 8. The cross-section is considered circular as determined by the pupillary aperture. An image 0.01 mm. in diameter upon the retina would normally be formed

by a circular disk 10 mm. in diameter viewed at a distance of about 15.5 meters. The refraction from the cornea into the aqueous humor is disregarded owing to the very small difference between their refractive indices; that is, for the purpose of computation, the aqueous humor is considered as extending to the anterior surface of the cornea. The thickness of the cornea is shown to scale by the dashed line drawn parallel to its anterior surface. The eye becomes shorter and the lens thicker when accommodated for near vision.

The mean energy-density in various vertical layers of the eye-media under the above conditions is shown in figure 9. Curve A represents

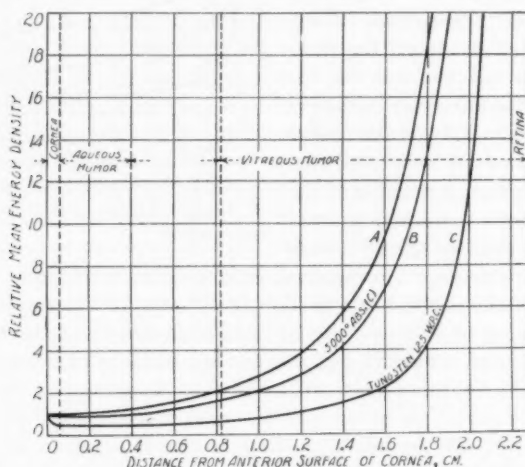


Fig. 9. Energy-density in the useful beams of light from a small source (distant vision).

the relative energy-density in various parts of the beam if there were no absorption of energy by the eye-media. If the small disc be diffusely and totally reflecting and be illuminated by radiation from a black-body at 5000° absolute, the mean energy-density in various parts of the path of the beam is represented by curve B, after allowing for absorption. Curve C represents the conditions when the illuminant is a vacuum tungsten lamp operating at 7.9 lumens per watt. It is seen, as might be expected, that the mean energy-density becomes relatively high near the retina. There is quite a uniform mean energy-density, however, for more than half of the distance of the path in the eye. This is

due to the fact that the absorption of energy in the eye-media approximately overcomes the concentrating effect of refraction. In the case of curve *C*, this absorption more than overcomes any concentrating action for one-half the distance. In order to compare curves *B* and *C* on a basis of mean energy-density per lumen, the ordinates of curve *C* must be multiplied by a factor approximately equal to thirty. In other words, the energy-density is about the same for a beam of tungsten radiation (7.9 lumens per watt) containing one unit of light flux as for a beam of radiation (of the same area of cross-section) from a black-

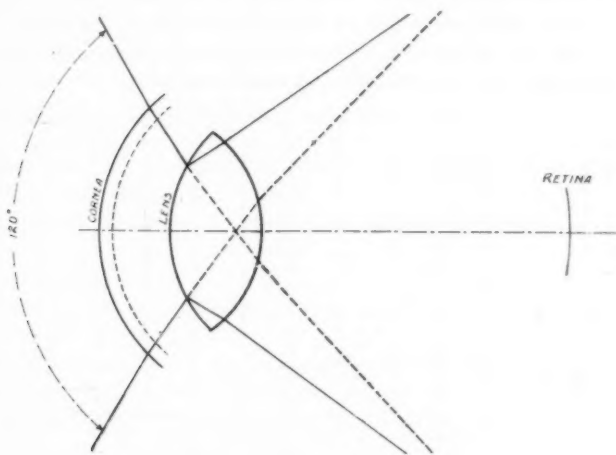


Fig. 10. Path of light in the eye (extended object).

body at 5000° absolute containing about thirty units of light flux. The energy-density curves are practically the same for near vision as for distant vision, and hence they have not been plotted.

Before discussing the foregoing further, it is of interest to consider the other extreme case—namely, when the object subtends a large angle. The entire visual field subtends approximately a solid angle of 120°. The useful beam of radiation included within a solid angle of 120° at the eye is shown by the full lines in figure 10, when the eye is accommodated for a reasonably near vision. If the object that is being viewed be illuminated with the same density of radiation of the same spectral character as the object considered in figure 8, it is obvious that the brightness of the retinal image will be the same and a much greater

amount of energy will pass through the pupillary aperture. In other words, the energy-density at the retina will be the same in the two cases, but the energy-density in the lens and anterior section of the eye will be many times greater in the case of the extended source. The ratio of the energy-densities in the plane occupied by the pupillary aperture will be approximately equal to the ratio of the solid angles subtended by the sources. In the two cases considered, when the brightnesses of the retinal images are equal, the energy-density in the pupillary plane for the case of the extended source is several million times greater than in the case of the small source. This is shown diagrammatically in figure 11 for equal energy-densities at the retina—that is, for equal brightnesses of the retinal images. Curve *D* represents the condition for the extended source and curve *E* for the small source.

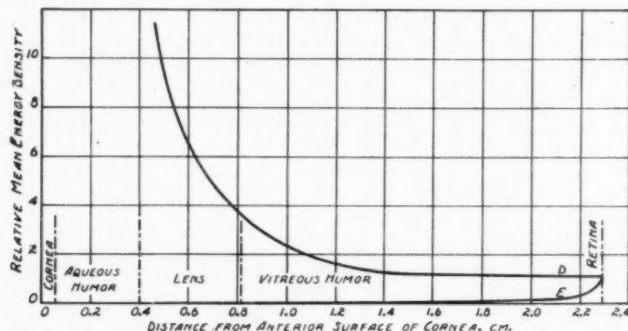


Fig. 11. Energy-density in the useful beams of light from sources subtending large, *D*, and small, *E*, solid angles.

The foregoing conditions are of importance in many cases of vision if eye-fatigue or cataract is to be attributed to the absorption of energy. For instance, a small area of molten glass or metal may appear quite harmless. A larger area of equal brightness should appear equally harmless, but, as is evident from the foregoing, the actual energy-density in various parts of the beam would be far different in the two cases. In the case of a large area the energy-density in the lens would be many times greater than in the case of the small area. In ordinary vision there are many cases of extended areas of comparatively high brightness, such as a snow field, a desert, the sky, the walls of a room and pavements.

It is of interest to consider the possible effect of sunlight (radiation approximately like that presented for a black-body at 5000° absolute), but in doing so allowance must be made for the absorption of radiant energy by the water-vapor in the atmosphere. It has been observed that water-vapor is somewhat more transparent to the sun's radiation than is water in the liquid state. Assuming that the absorption of the water-vapor existing in the atmosphere is equivalent to a layer of the liquid 1.5 cm. in thickness, and with due consideration of the relative luminous efficiencies of a black-body at the apparent temperature of the sun and of the tungsten lamp, it is found that approximately a hundred times as much energy is absorbed by the eye per lumen of tungsten light as per lumen of sunlight. But it is not uncommon to find sunlight intensities far greater than a hundred times that encountered with artificial light under working conditions. In fact, the ratio of actual working intensities is often greater than 1000 to 1. This indicates that eye-fatigue and cataract should be quite noticeable under natural lighting conditions if they can be attributed to an energy effect. In fact, cataract is quite prevalent in India, but in this case, according to the work of Burge (4), the cause might be traced to an accumulation in the liquids of the body of something which so modifies the lens protein that energy of certain short wave-lengths can precipitate it, thereby causing opacity.

To summarize, it is shown that when viewing luminous objects of small area (subtending a small solid angle) there is no serious concentration of energy in the eye-media until the retina is approached. However, when viewing extended objects (large solid angle) there is a relatively much greater energy-density in the lens and anterior parts of the eye than in the posterior portions. When the retinal images are of the same brightness, there will be a very much greater energy-density in the lens when viewing an object subtending a large solid angle than when the object subtends a small angle if the spectral character of the illuminant and the intensity of the illumination are the same. This indicates that large sources of radiation of a relatively low visual brightness might be effective in forming cataract or causing eye-fatigue if the "absorption-of-energy theory" is correct. In fact, if the deterioration of the lens is due to ultraviolet rays, the latter might be present in such small amounts as to appear harmless, but when it is recalled that the energy-density in the lens is very high when viewing extended objects, such as the sky, pavements, surfaces of molten glass, metal, etc., it appears to be possible that the ultraviolet rays still might be present in

sufficient amount to do damage. From this standpoint sunlight, owing to the greater intensities encountered, appears to be probably as effective in producing cataract and eye-fatigue as ordinary artificial illuminants and some industrial processes, even after allowing for the higher luminous efficiency of the former and the absorption of energy by the water-vapor present in the atmosphere.

It is not claimed that the data in this paper settle the question of the influence of energy absorption in the eye-media. The object has been to show in what relative quantities the energy is absorbed in the various parts of the eye and also the energy-density in the path of the useful beam of radiation in order that those interested in eye-fatigue and cataract might have these quantitative data available.

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STUDIES ON THE CONDITIONS OF ACTIVITY IN ENDOCRINE GLANDS

V. THE ISOLATED HEART AS AN INDICATOR OF ADRENAL SECRETION INDUCED BY PAIN, ASPHYXIA AND EXCITEMENT

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Knowledge of the conditions under which the endocrine glands become active or manifest increased activity is important for several reasons. Such knowledge is valuable as an extension of our acquaintance with a realm of physiology which is still largely unexplored. It permits correlated studies of other bodily processes which vary under the same conditions. And it gives a basis for inquiry into the functions performed by the endocrine glands, for the service of an organ should reasonably be looked for in relation to the times of its special activity. With such ideas in mind, the present series of studies was entered upon.

In two papers published in 1911, Cannon, in collaboration with de la Paz (1) and with Hoskins (2), brought forward evidence that the adrenal medulla was stimulated to secrete by emotional excitement, by "pain" and by asphyxia. Adrenal secretion had previously been proved to be subject to sympathetic stimulation by way of the splanchnics; and as excitement, pain and asphyxia were conditions well recognized as accompanied by sympathetic activity (manifested, e.g., by inhibition of digestive functions), an attendant adrenal secretion was naturally to be expected. In a series of papers which followed these first two, experiments were described showing that adrenal secretion was serviceable in lessening muscular fatigue (3) and in accelerating coagulation of the blood (4). An interpretative paper (5) pointed out that excitement, pain and asphyxia were conditions which in natural existence would commonly be associated with struggle, and that the visceral changes, including adrenal secretion, which accompany these three states, would be useful in great muscular effort. This interpretation presented a new view of the function of the sympa-

thetic division of the autonomic system and of the adrenal medulla in important bodily adjustments.

Within the past few years both the evidence on which the foregoing interpretation was based and the interpretation itself have been seriously questioned. In an extensive series of papers, Stewart and Rogoff have reported apparently careful quantitative studies on the rate of adrenal discharge, and have drawn the conclusions that the discharge is continuous, that in any animal it is approximately constant, and that the supposed variation is dependent on the rate at which the blood flows through the lumbo-adrenal veins (6). They found no increase of secretion in pain (7), asphyxia (8) or emotional excitement (9). More recently Gley and Quinquaud have also examined experimentally adrenal secretion and have come to the decision that adrenin is not secreted in sufficient amount to be carried effectively to the organs on which it may act, and that therefore no true physiological adrenalinemia exists (10). The sharp difference between the views put forth by Cannon and his coworkers and the ideas supported by these later investigators warrants a reëxamination and a thorough testing of the evidence for adrenal secretion in pain, asphyxia and excitement.

REVIEW OF THE POSITIVE EVIDENCE

1. *That adrenal secretion is induced by sensory stimulation.* In the original tests Cannon and Hoskins (2) made use of rhythmically contracting segments of rabbit intestine suspended lengthwise in a glass cylinder through which oxygen was passed. The segment, when not surrounded by the blood to be tested, was bathed in Ringer's solution. The test blood, the cylinder and the fresh Ringer's solution were all kept at body temperature in a common bath. The blood to be tested was taken before and after the experimental procedures by passing a catheter through a nick in the femoral vein into the iliac and thence into the inferior vena cava anterior to the entrance of the lumbo-adrenal veins. A thread tied tightly around the catheter marked the point to which it was inserted and permitted reinsertion to the same point in subsequent sampling of the blood. The position of the catheter opening, which was at one side, was kept constant by attention to the position of the knot in the thread. Thus both the control blood and the blood after stimulation were taken as exactly as possible from the same region. Under these circumstances normal blood removed before stimulation of the central end of the sciatic nerve caused no inhibition

of the rhythmically contracting intestinal segment, whereas that removed afterwards produced a marked relaxation. The conclusion was drawn that the adrenal glands are affected through nervous channels when a sensory trunk is strongly excited and that they then pour into the blood stream their secretion.

The foregoing conclusion was supported a year later (1912) by Anrep who found that the denervated limb or kidney at first expands but later quickly contracts when the central end of the cut sciatic nerve is stimulated (11). If the adrenal glands were removed or the splanchnic nerves were cut, the phase of contraction disappeared. Since the organs (limb or kidney) were denervated, the only factor which could cause their contraction in the presence of a rise of general blood pressure must be some agency brought by the blood stream; and since the phenomenon disappeared on exclusion of the adrenals, the conclusion was drawn that adrenal secretion, poured out in consequence of reflex stimulation through the splanchnics, produced the observed vasoconstriction.¹ The observations of Anrep on the denervated limb have recently been confirmed by Pearlman and Vincent (12).

The following year (1913) Levy reported the incidental observation that after both stellate ganglia had been removed and both vagus nerves cut, stimulation of the sciatic nerve occasioned irregularity of the heart (13). He also noted that excitation of the peripheral end of the cut splanchnic would cause the same cardiac changes, and that they did not occur if the adrenal gland was removed on the stimulated side. He therefore concluded that on sciatic stimulation the denervated heart was being affected by adrenin discharged reflexly.

In 1917 Florovsky (14) undertook an investigation of a strange fact previously observed by Ostrogorsky, which was that if the cervical sympathetic and the chorda tympani nerves are severed, and the secretory effect of a dose of pilocarpin is disappearing, sciatic stimulation causes a considerable increase in the flow of saliva. The effect was so striking that he looked for a third nerve to the submaxillary gland but could not find it. Under the conditions described by Ostrogorsky, Florovsky succeeded in producing augmented salivary secretion

¹ In the same year with Anrep's observation, Elliott reported (*Journ. Physiol.*, 1912, xliv, 406) exhaustion of the adrenal gland with intact nerve supply when the sciatic nerve was stimulated periodically for four hours. Since Elliott's methods were concerned with a quantitative assay of the amount of adrenin left in the gland after stimulation, and not directly with adrenal secretion, his results will not be considered in the present review of the evidence.

by stimulating the peripheral end of the cut splanchnic and by intravenous injection of adrenin. He also confirmed Ostrogorsky's observation of an augmented flow after sciatic stimulation. This reflex secretion did not occur, however, if both adrenal glands were extirpated, or if one was extirpated and the vein of the other obstructed, or if both splanchnic nerves were cut. He concluded, therefore, that the anomalous secretion from the denervated submaxillary gland is due to adrenal secretion resulting from reflex stimulation.

The foregoing evidence, involving tests made on blood removed from the body, and tests made in the body on the denervated limb, the denervated kidney, the denervated salivary gland and the denervated heart, are harmonious in testifying to a reflex discharge of the adrenal glands when a sensory nerve is stimulated.

2. *That adrenal secretion is induced by asphyxia.* In their examination of the effect of asphyxia on adrenal secretion, Cannon and Hoskins (2), in 1911, used the same methods that were employed for testing the effect of sensory stimulation. In the course of the examination it was discovered that *extreme* asphyxia would cause a change in the blood which would produce the same effect as adrenin on the beating intestinal strip, i.e., inhibition, and this even though the adrenal glands were carefully removed or the circulation confined to the region above the diaphragm. This observation indicated the necessity for careful control at the time the asphyxial blood was taken. Accordingly, after *moderate* asphyxia, there was removed from the femoral vein blood which should serve as a control sample of the systemic venous flow below the entrance of the lumbo-adrenal veins; and at as nearly as possible the same time another sample was removed from the inferior vena cava at a point anterior to the opening of these veins. This latter blood caused the typical inhibition indicating the presence of adrenal secretion, whereas the control femoral blood, like the vena cava blood taken before asphyxia, failed to cause inhibition. Through the use of the control, therefore, the presence of an accessory factor, simulating the action of adrenin, was ruled out. Consequently the conclusion was drawn that asphyxia results in secretion of the adrenal glands.²

² At about the same time that the paper by Cannon and Hoskins was published, Starkenstein (Zeitschr. Exper. Path. Therap., 1911, x, 78) reported that in one rabbit asphyxia caused nearly an abolition of the color reaction of the adrenal gland connected with the central nervous system, whereas the other gland, with its nerve severed, showed a good color reaction. In 1912, Borberg (Scand. Arch.

In 1912 Anrep (11) noted that a decrease in volume of the denervated limb and denervated kidney occurred during asphyxia, in spite of a general rise of arterial pressure, just as he had seen it occurring as a consequence of sciatic stimulation. This vascular constriction appeared, however, only when the adrenal glands were connected with the circulation and the splanchnic nerves were intact. When the adrenal glands were out of circulation, asphyxia caused some rise of arterial pressure, though less than in the intact animal, but no constriction in the vessels of the denervated limb or kidney. He concluded, therefore, that the adrenal glands are excited during asphyxia. These observations of Anrep on the constriction of the vessels in the denervated limb were at once confirmed by Itami (15), who found that it did not occur after transection of the cord. Since the constriction was not due to the direct action of CO_2 on the vessel wall, nor to reaction of the vessels to an increased internal pressure, he interpreted the result as due to increased adrenal secretion.

In 1914 Gasser and Meek, while making observations on a dog with stellate ganglia removed and the vagi cut, noted, when the animal was asphyxiated for 30 seconds, an acceleration of the heart beat amounting to 92 beats per minute (16). Now, under ether anesthesia, the blood vessels of the adrenal glands were tied. After recovery from the operation, asphyxia lasting 90 seconds caused an acceleration of only 8 beats per minute.

In 1917 Gley and Quinquaud found an amount of adrenin in adrenal venous blood obtained during asphyxia considerably in excess of that obtained when the animal was undisturbed (17). Using the rise of blood pressure as a test, they determined that from 4 to 8 cc. of the asphyxial adrenal blood were equivalent to 16 cc. of the blood before asphyxiation. In their experiments injection of 20 cc. of blood from the inferior vena cava, taken above the adrenal veins after 3 or 4 minutes of asphyxia, caused a rise of arterial pressure from 24 to 45 mm.

Physiol., xxviii, 124) quoted Fridericia as having performed six experiments on guinea pigs poisoned with an excess of CO_2 with some diminution of the chrome reaction in the glands. In the same year, Kahn (Arch. f. d. gesamt. Physiol., 1912, cxlvi, 578) reported asphyxia in monkeys as causing a marked difference in the adrenin content of the two adrenal glands, one of which was removed before asphyxia, the other afterwards. The adrenin present was quantitated by the use of Laewen's preparation. Since these observations, although they support the view that asphyxia causes adrenal secretion, are really assays of the amount of adrenin left in the gland after asphyxia, and do not give direct indication of adrenal activity, they will not be further considered in the present paper.

higher than that produced by injecting an equal quantity of cava blood taken from the same level before asphyxia.³

The foregoing evidence which, like that obtained after sensory stimulation, was the result of studies by various observers using a variety of methods, is harmonious in leading to the conclusion that adrenal secretion is increased by the asphyxial state.

3. *That adrenal secretion is induced by excitement.* In the experiments on the influence of emotional excitement, performed by Cannon and de la Paz in 1911 (1), the methods employed were similar to those used by Cannon and Hoskins. The only differences were that the animals did not receive a general anesthetic and that the catheter was introduced under local anesthesia. Controls were obtained in every instance. As the original records show, after emotional excitement the blood drawn from the inferior vena cava anterior to the opening of the adrenal veins repeatedly caused inhibition of the beating intestinal strip, whereas that removed before excitement had no such effect. Since excitement after removal of the adrenal glands did not yield this result, and since the effective blood lost its inhibitory power when exposed to oxygen (a procedure known to destroy adrenin), the inference was drawn that adrenal secretion is stimulated by great emotion.

These conclusions were confirmed in 1913 by Hitchings, Sloan and Austin (18), who used the same method to obtain blood and the same test for adrenin that Cannon and de la Paz had used. They found that after great fear and rage had been induced in a cat by the attempt of a muzzled dog to fight it, the adrenin reaction was clearly demonstrable. The reaction did not occur, however, if the splanchnic nerves had been previously severed.

In 1918 Redfield reported that in the horned toad nervous excitement causes a contraction of the melanophores in the denervated skin, a reaction which does not occur after the removal of the adrenal glands (19).

In addition to these direct observations on the stimulating effect of strong emotion on adrenal secretion, there were other observations having inferential value. In 1914 Cannon and Mendenhall, after show-

³ Gley and Quinquaud express the opinion that the experiments of Cannon and Hoskins were indecisive in determining the effect of asphyxia on adrenal secretion, because relaxation of the intestinal strip could be induced by blood removed from the asphyxiated animal after the adrenals had been excised. They seem not to have paid attention to the control observations which Cannon and Hoskins were careful to make (see p. 402).

ing that clotting of the blood is hastened by stimulation of the splanchnic nerves, found that great excitement will cause the same effect (4). The evidence which they brought that injected adrenalin shortens the clotting time, that when the splanchnic nerves are stimulated the adrenal glands are necessary for the effect, and that excitement induces faster clotting only so long as the splanchnic nerves are intact, was confirmatory of the view that excitement causes adrenal discharge.

In 1915 Lamson noted that injection of adrenalin would cause a polycythemia, and that emotional excitement, such as fear and rage, would likewise cause it (20). If an animal was frightened after removal of the adrenal glands, however, there was no increase in the red count. Lamson observed that asphyxia had the same effect as fright and that removal of the adrenals prevented the customary increase seen after asphyxiation.

By both direct and indirect testimony, offered by different observers using different methods, the evidence is concordant that emotional excitement is accompanied by increased secretion of the adrenal medulla.

All of the observations cited above, leading to the conclusion that adrenal secretion is increased in pain, asphyxia and excitement, were on record before the negative results of recent investigations were published. These positive data have all been consistent, they were obtained by a number of quite independent workers, and they were the outcome of a variety of operative procedures each differing from those yielding the negative results. In view of these facts it would appear that this body of cumulative testimony deserved more consideration than it received, and warranted a comparison of experimental methods.

A CONSIDERATION OF CRITICISMS OF THE CATHETER METHOD

In criticism of the catheter method used by Cannon and Hoskins, Stewart and Rogoff declare first, that the results obtained by it are valid only if the blood flow is assumed to be constant during the whole experimental period; and second, that the method does not permit any judgment on this point (7). Thus, if there be a continuous secretion of adrenin undisturbed by reflex stimulation, as they maintain is the case, there could be an increased concentration only if the blood flow through the adrenal vessels were retarded. There is another possibility, however, which should be considered. The blood flow through the adrenal vessels might be *increased*. Strong sciatic stimu-

lation has a well-known pressor effect. This may be due largely to reflex splanchnic stimulation. But there is no evidence that splanchnic stimulation causes constriction of adrenal vessels. Indeed, the careful observations of Burton-Opitz and Edwards (21) have shown that stimulation of the splanchnic nerves causes a greater blood flow through the adrenal vein, a result which Biedl had previously noted (22). With a heightened general blood pressure and at least no constriction of the adrenal vessels, the blood flow through these vessels must necessarily be increased. Under these circumstances, on the basis of Stewart and Rogoff's argument, the adrenin would be more *dilute* rather than more concentrated in the adrenal blood. A faster flow in the inferior cava which might accompany the higher arterial pressure would still further dilute the secreted adrenin. With heightened arterial pressure, therefore, the conditions which would prevail in the inferior cava anterior to the adrenal veins would be highly unfavorable for demonstrating a greater concentration of adrenin, if adrenal secretion were constant and unvarying. The positive evidence which was obtained that adrenin is actually *concentrated* in the circulating blood at this point in times of stress indicates, definitely, an increased secretion from the glands.

The suggestion that the positive results obtained by Cannon and his collaborators might have been due to a fortunate location of the eye of the catheter (7) seems to have been made with disregard for the care exercised in making control observations under precisely the same conditions before and after stimulation.

Stewart and Rogoff's few attempts to obtain reactions from intestinal strips by use of blood taken by catheter from the inferior cava were unsuccessful (7). They explain their lack of success by supposing that the adrenal secretion was too highly diluted by cava blood. Without direct observation of their technique it is difficult to suggest the reason for their failure to obtain the positive results undoubtedly demonstrated by the catheter method. It may be stated, however, that the method is difficult and exacting, and that not until after some experience with it did it begin to yield us positive results.

THE DENERVATED HEART AS AN INDICATOR OF ADRENAL SECRETION

The difficulties encountered in testing for adrenin in blood removed from the body render desirable a simpler method which will yield reliable results in the hands of any competent experimenter. In 1917 Cannon (23), making use of the hint offered in the incidental observations of

Levy (13) and of Gasser and Meek (16), suggested the employment of the completely denervated heart to demonstrate an increase of adrenin in the circulating blood.⁴

This is a preparation which is likely to be highly serviceable in the further elucidation of adrenal function. In the first place, the preparation has important advantages dependent on testing the blood while it is still in the body—advantages which were praised by Stewart and Rogoff (7), but which were lacking in their use of the intestine and uterus as indicators. These advantages are: security against loss of adrenin in manipulation, avoidance of a development of the pressor property of clotted blood, exclusion of the possible effects on secretion of loss of blood or adrenin from the organism, and finally the possibility of direct quantitative comparison of adrenal secretion induced by successive stimulations. Further, the denervated heart is an organ highly sensitive to adrenin; intravenous injection of adrenalin at the rate of 0.001 mgm. per k. per minute has increased the heart rate as much as 28 beats per minute. Moreover, the method permits a graphic record from which may be judged the latent period and the duration of secretion of the adrenal glands in consequence of stimulation. And finally, the necessary operation (severance of the vagus nerves and removal of the stellate ganglia between the first two ribs on either side) is so simple that anyone inclined to doubt that more adrenin is secreted, in consequence of reflex or other stimulation, may readily make the test.

Sensory stimulation. In a cat under urethane, with vagi cut and stellate ganglia excised, stimulation of the central end of the cut sciatic will cause the heart rate to increase in some instances as much as 50 beats a minute.⁵ Comparisons of the increased rate due to sciatic stimulation with the effects of adrenalin (quantitated as base) injected intravenously indicate that the range of reflex adrenal secretion lies

⁴ At the same time Cannon reported (*Science*, May, 1917, xlv, 463) that the denervated heart revealed an increase of adrenal secretion after sciatic stimulation or asphyxiation, and promised a full report of the experiments in this Journal. Absence from the United States for nearly two years has unavoidably delayed the complete paper until this time.

⁵ Many years before Levy's observation, Hunt noted (*this Journal*, 1899, ii, 444) that stimulation of a sensory nerve would cause cardiac acceleration after all cardiac nerves were divided, and that the same result followed stimulating the peripheral splanchnic. It differed from the acceleration following sympathetic stimulation by beginning slowly, i.e., about ten seconds after the start of stimulation. It is interesting to observe that this period is almost exactly that required for the distribution of adrenal secretion by the circulating blood.

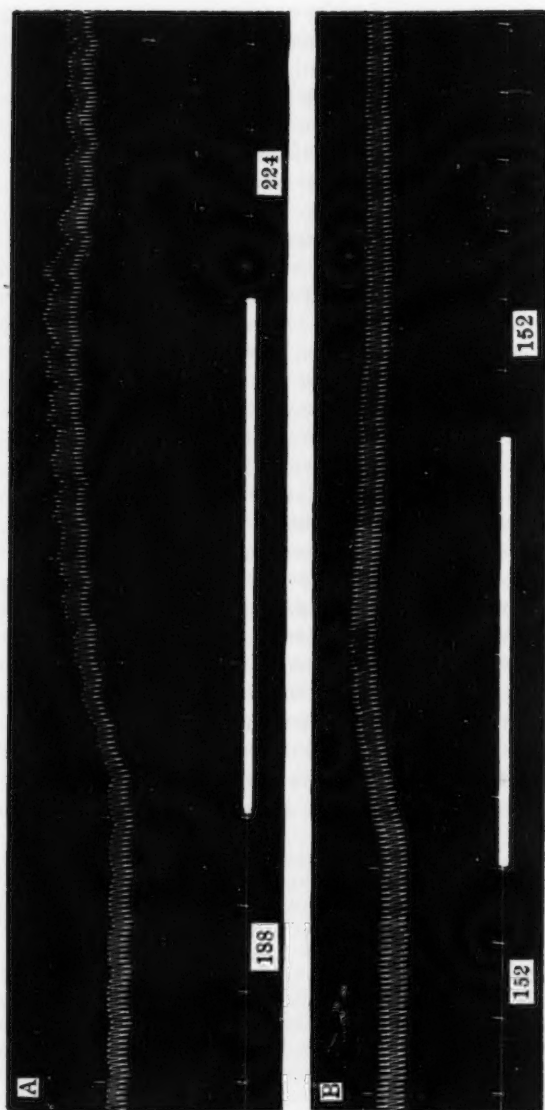


Fig. 1. Records of the beat of the denervated heart, membrane manometer. Time intervals, 5 seconds.

A, Sciatic stimulation 30 seconds, 2:21. Increase of rate from 188 to 224 per minute. (Adrenal glands tied off, 2:52).
B, Sciatic stimulation 30 seconds, 3:10. No increase of rate.

TABLE I

Examples of increased rate of the denervated heart on sciatic stimulation

DATE	TIME	SCIATIC STIMULATION	RATE BEFORE	RATE AFTER	INCREASE PER MINUTE
March 21.....	2.58	30 seconds	220	264	44
	3.04	30 seconds	220	256	36
	3.15	15 seconds	212	240	28
	3.16	Splanchnics cut			
	3.25	30 seconds	184	192	8
	3.28	15 seconds	184	192	8
March 23.....	2.16	30 seconds	176	228	52
	2.21	30 seconds	188	224	44
	2.52	Adrenal glands tied			
	3.07	15 seconds	152	156	4
	3.10	30 seconds	152	152	0
April 6.....	2.31	30 seconds	216	240	24
	2.39	30 seconds	212	236	24
	3.12	30 seconds	184	208	24
	3.15	30 seconds	196	216	20
April 7.....	2.50	30 seconds	200	236	36
	2.52	30 seconds	200	224	24
	2.56	30 seconds	200	244	44
	3.01	30 seconds	200	240	40
	3.05	Cerebrum removed			
	3.19	30 seconds	208	236	28
April 21.....	1.01	45 seconds	144	180	36
	1.05	55 seconds	152	184	32
	1.14	55 seconds	156	180	24
	1.20	55 seconds	156	180	24
	1.33	50 seconds	162	192	30
	1.54	Right adrenal tied, left splanchnic cut			
	2.06	45 seconds	164	164	0
May 7.....	10.35	30 seconds	156	180	24
	10.43	40 seconds	156	180	24
	10.47	45 seconds	156	180	24
	11.03	Both adrenals removed, 100 cc. gum-salt solution			
	11.07	40 seconds	174	174	0
	11.10	40 seconds	138	138	0

between 0.001 and 0.005 mgm. per k. per minute—i.e., from five to twenty-five times the amount regarded by Stewart and Rogoff as the normal output. Reflex increase of the cardiac rate does not occur if the adrenal glands are removed (see fig. 1 and table 1).

Asphyxia. Asphyxiation of the cat with the heart completely denervated will cause a noteworthy increase in the heart rate (see fig. 2 and table 2), an effect not seen after adrenalectomy. The figures in table 2 illustrate another point mentioned in 1917, viz., that an indication of adrenal secretion may be obtained from the denervated gland if asphyxia is prolonged. In the experiment of February 24, for example, asphyxia for 20 seconds, though previously effective, caused no change after severance of the splanchnics. In that of February 27, asphyxia of 60 seconds caused no change after splanchnic section; and in that of February 28, though asphyxia of 35 seconds had been highly effective before the splanchnics were cut, thereafter asphyxia of 45 seconds increased the heart rate only 4 beats per minute, whereas asphyxia of 90 seconds caused an increase of 68 beats a minute. Similar differences are observed in the experiment of March 21. Unfortunately these observations were not checked by final proof that cutting the splanchnics completely denervated the glands, though the marked drop in pulse rate may be regarded as testimony to that conclusion. The results are in agreement, however, with evidence adduced by Czubalski (24) that asphyxia, if sufficiently prolonged, may have a direct stimulating action on the adrenal medulla, and perhaps on other chromaffine tissue as well.

In 1917 Cannon described another method of demonstrating adrenal secretion, which consists in cutting all the nerves in the gastro-intestinal mesentery, tying all the limb arteries and the carotids, and thus leaving the circulation confined chiefly to the splanchnic area which, however, is denervated (23). Under these circumstances it is not uncommon for asphyxia to cause a slight rise of pressure after an interval of 40 to 60 seconds and a very considerably greater rise as soon as respiration begins again; these results do not occur if the adrenal glands are excluded (see fig. 3).

Emotional excitement. The completely denervated heart can be used as an indicator of adrenal secretion in testing the influence of emotional excitement quite as well as in testing the influence of sensory stimulation and asphyxia. It is only necessary to take somewhat greater pains in order to keep animals in normal condition after operation. To denervate the heart, the stellate ganglia are first removed

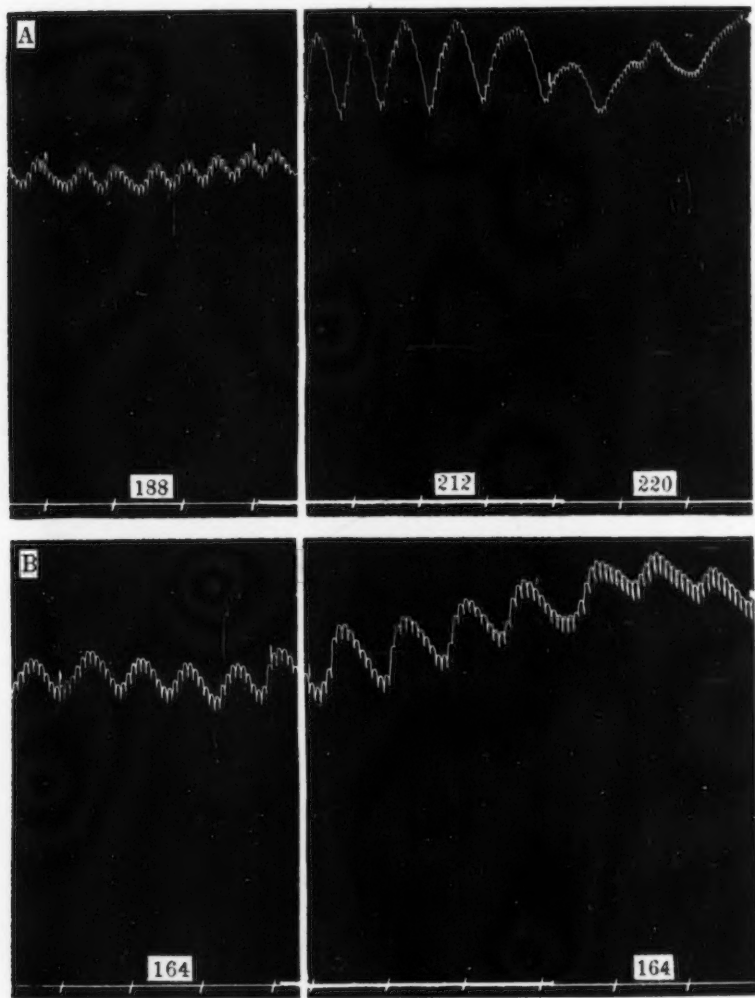


Fig. 2. Beginning and end of records of the beat of the denervated heart, mercury manometer. Original size. Time intervals, 5 seconds.

A, Asphyxia 60 seconds, 3:55. Increase of rate from 188 to 220 per minute. (Adrenal glands tied off, 4:45).

B, Asphyxia 60 seconds, 4:50. No increase of rate. Blood pressure rose from 92 to 124 mm. Hg.

TABLE 2

Examples of increased rate of the denervated heart on asphyziation. (In the first five cases the abdomen had been opened)

DATE	TIME	ASPHYXIA	RATE BEFORE	RATE AFTER	INCREASE PER MINUTE
January 25.....		80 seconds	240	256	16
		Adrenals removed			
		90 seconds	192	192	0
February 17.....	2.50	60 seconds	162	202	40
	2.58	60 seconds	158	200	42
	3.01	Veins tied both sides of adrenal glands			
	3.04	60 seconds	166	206	40
	3.10	Adrenal glands tied off completely			
	3.18	60 seconds	146	146	0
February 24.....	3.35	40 seconds	204	256	52
	3.38	20 seconds	216	228	12
	4.10	Splanchnics cut in thorax			
	4.15	20 seconds	204	204	0
February 27.....	3.28	90 seconds	208	236	28
	3.41	Splanchnics cut in thorax			
	3.43	60 seconds	188	188	0
February 28.....	11.39	35 seconds	180	212	32
	12.08	Splanchnics cut in thorax			
	12.10	45 seconds	164	168	4
	12.13	90 seconds	156	224	68
	12.18	90 seconds	172	224	52
	12.25	Veins tied both sides of adrenal glands			
	12.31	90 seconds	168	180	12
March 16.....	2.51	60 seconds	196	212	16
	3.05	45 seconds	208	228	20
	3.59	90 seconds	188	224	36
March 21.....	3.09	45 seconds	220	240	20
	3.20	Splanchnics cut in thorax			
	3.30	90 seconds	180	212	32
	3.35	45 seconds	176	188	12
March 23.....	2.24	60 seconds	192	236	44
	2.34	Abdomen opened	192	204	12
	2.53	Adrenal glands tied off completely			
	3.20	60 seconds	152	156	4

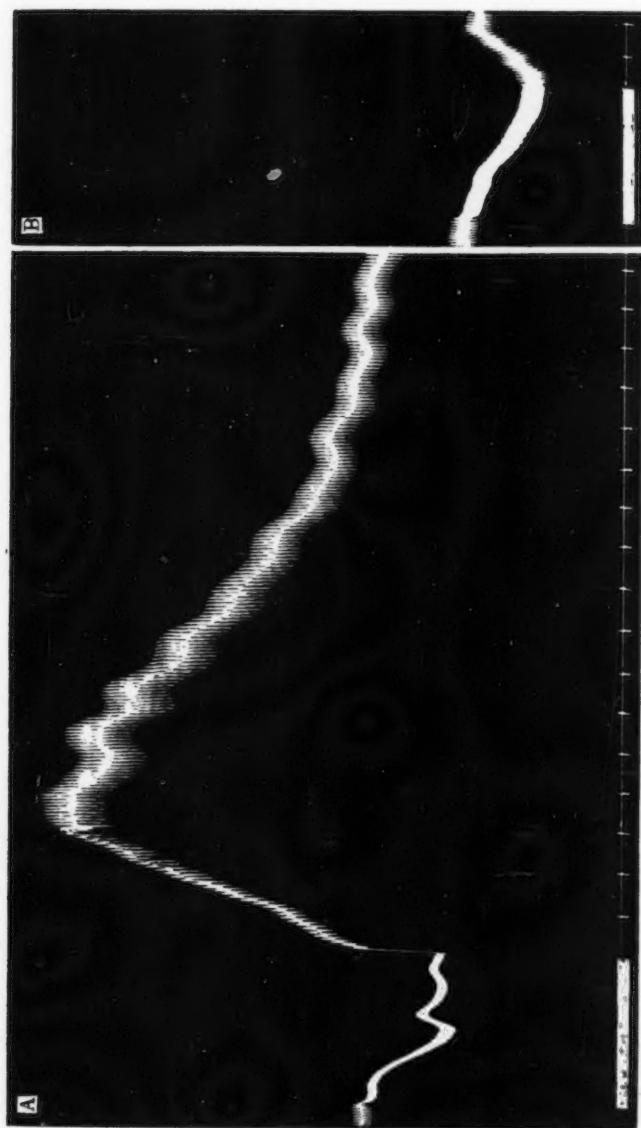


Fig. 3. Blood pressure record after tying the carotid, subclavian and iliac arteries and denervating the splanchnic area. Original size. Time intervals, 30 seconds.

A, Asphyxia 2 minutes. Rise of pressure at end of 1 minute and again after asphyxia period. (Adrenals then tied off).

B, Asphyxia 2 minutes. Both rises absent.

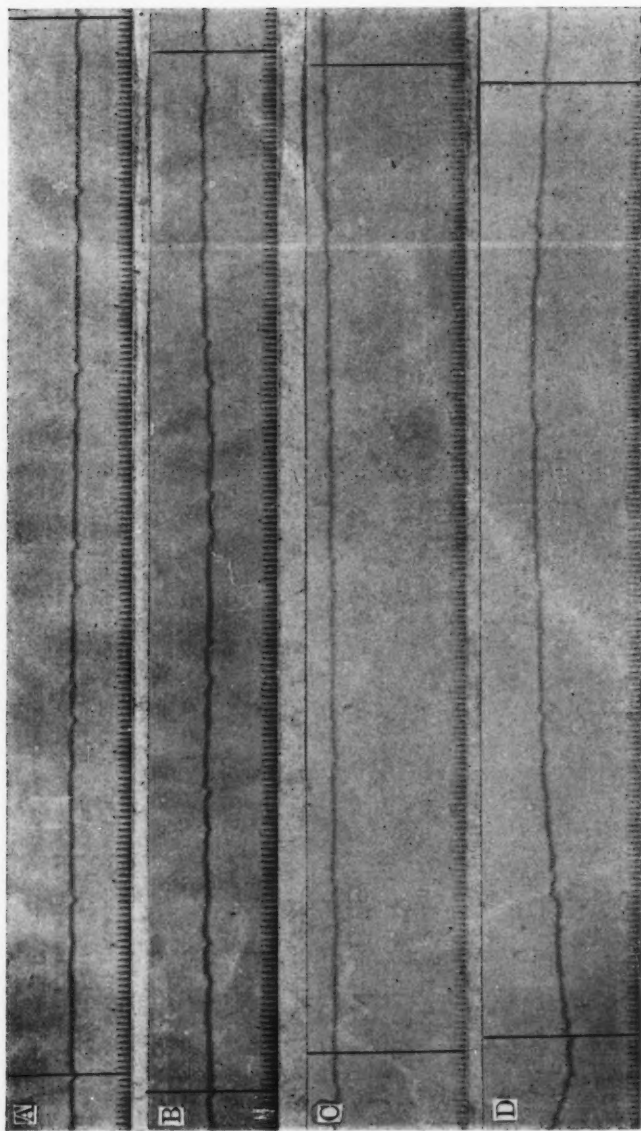


Fig. 4. Electrocardiograms of the denervated heart. Time intervals, 1/100 second. Above the time record the small dots mark 1/10 second.

A, Animal calm, heart rate 217 beats per minute. April 8.

B, Animal excited, heart rate 255 beats per minute. April 8. (Adrenal removal completed 9:50 a.m., April 10.)

C, Animal calm, heart rate 217 beats per minute. April 10, 2:40 p.m.

D, Animal excited, heart rate 221 beats per minute. April 10, 2:43 p.m.

under ether with aseptic precautions; later the right vagus nerve is severed below the recurrent laryngeal branch; and still later, the left vagus nerve is cut in the neck. The heart is thus wholly disconnected from the central nervous system and any agency causing an increase in the heart rate must exert its influence through the blood stream. In figure 4 are presented electrocardiographic records of the heart rate in a cat, operated upon as above described. The records show that with the adrenal glands normally innervated the rate was 217 per minute when the animal was calm, and 255 when excited. And after the adrenal glands were removed the rate when calm was 217 and when excited was 221.

The results obtained with the isolated heart used as an indicator of adrenal secretion thus confirm in every respect the results obtained eight years ago by the catheter method.

Care in assuring isolation of the adrenal glands. If the splanchnic nerves are severed or if the adrenal gland is removed on one side and the splanchnic fibers are cut on the other, as Stewart and Rogoff have noted, adrenal secretion may be isolated from nervous control in most cases, but there is not absolute certainty that this procedure will wholly eliminate nervous influences (29). For example, in one case, after the heart was wholly denervated, sciatic stimulation for one minute increased the rate from 220 to 264 beats per minute. The splanchnic nerves were then isolated in the thorax and cut. In two minutes the heart rate had dropped down to 192 beats per minute. Sciatic stimulation now increased the rate to 204, i.e., a rise of 12 beats per minute.

Similar observations have been made on animals with denervated heart that have been kept alive and observed under excitement. In one such case there was an increase of 42 beats per minute, although the left adrenal gland had been removed and the right splanchnic cut in the abdomen on the previous day. After removal of the right gland excitement had no effect. In another instance in which a similar operation had been performed there was an increase of approximately 28 beats a minute during excitement, an increase which disappeared as soon as the remaining adrenal gland was excised and the animal allowed to recover from etherization. It is possible, therefore, that other fibers than those contained in the splanchnic supply, or that occasionally, perhaps, a crossing of fibers from one splanchnic supply to the gland of the other side of the body, may be present in the cat and may thus lead to erroneous conclusions.

It has been assumed that by tying the adrenal veins at their junction with the inferior cava and the lumbar veins as they approach the adrenal glands, all possibility of an entrance of adrenal secretion into the blood stream has been excluded (10). That this may be a reasonable assumption in most cases was shown by Flint's studies of the blood supply of the cortex and medulla, which brought out the fact that the vessels of the two parts of the gland are separate. He reported, however, that as a variation from the usual condition, anastomosis may be present between the branches of the venous tree in the adrenal medulla and the venous plexus of the capsule (25). Under these circumstances the blood might flow from the medulla to the venous plexus which normally empties into the renal, phrenic and lumbar veins, into the *venae comites* of the suprarenal arteries, and to a less degree into the other veins. Further evidence of a direct vascular connection between the suprarenal gland and the veins of the kidney has been reported by Cow (26) who obtained an adrenal-like effect with blood taken from the kidney capsule of a cat.

In several instances in the course of the observations reported in this paper adrenal effects were seen after tying the lumbo-adrenal veins on both sides of the glands. In one case, after these veins had been thus tied, asphyxia caused the heart rate to increase from 166 to 206 beats a minute. The glands were then tied off completely, whereupon asphyxia had no effect (see table 2, February 17). In another instance, after the lumbo-adrenal veins had been carefully tied, injection of adrenalin into the vein as it crossed the gland caused a high rise of blood pressure, and in still another instance in which the veins were tied, splanchnic stimulation for 30 seconds caused the heart rate to rise from 172 to 248 beats per minute.

From these observations it is clear that conclusions based on results obtained when only the lumbo-adrenal veins are tied may lead to erroneous conclusions. The only absolutely safe method is that of excluding the glands from any possible action in the body by removing them or completely tying them off.

The gradual rise of pulse rate on repeated stimulation. A fact commonly noted in the course of the present experimentation was a gradual rise of the pulse rate with the lapse of time and with repeated indirect stimulation of the adrenal glands. In one instance an animal anesthetized with urethane had, after denervation of the heart, a pulse of 176 beats per minute. Repeated sciatic stimulation and asphyxia were accompanied by temporary increases of the pulse above the basal rate,

varying from 16 to 52 beats per minute. As these stimulations recurred, however, the basal rate gradually rose from 176 to 204. On tying off the adrenal glands completely, the rate fell to 152.

The increase of rate and its persistence at a progressively higher level with repeated stimulation are possibly facts of considerable importance in relation to the interaction of the endocrine glands, and deserve further examination.

A fall of pulse rate on sciatic stimulation. A curious fact noted in a number of instances after the abdomen had been opened was that sciatic stimulation, instead of causing an increase in the rate of the denervated heart, actually resulted in a slower beat. In one such case sciatic stimulation for 30 seconds reduced the rate from 216 to 212 beats per minute; subsequent stimulation for 45 seconds lowered it from 216 to 204, and still later from 236 to 216. In another instance sciatic stimulation lowered the rate from 216 to 212 and later from 232 to 212. No important changes of blood pressure preceded the altered rate. The significance of these effects is difficult to perceive. In the cases mentioned asphyxia caused a marked increase in the heart rate.

DEFENSE OF THE ISOLATED HEART AS AN INDICATOR OF ADRENAL SECRETION

In a recent paper on hyperglycemia, Stewart and Rogoff have incidentally offered four different arguments opposed to the conclusion that effects seen in the denervated heart are satisfactory proof of increased adrenal secretion (27). These arguments are as follows:

1. They state that there is nothing strange about an increase in the rate of the denervated heart when the central end of the sciatic or the peripheral end of the splanchnic nerve is stimulated—"it is obviously dependent upon the better blood flow through the coronary vessels." For evidence they cite Guthrie and Pike as having shown that in the perfused mammalian heart the rate could be made decidedly faster by raising the pressure of the perfusion fluid. In the experiments cited, however, Guthrie and Pike were using the *excised* heart; they definitely declare that the denervated heart *in situ* (the preparation described in this paper) does not follow the law of the excised heart as regards pressure changes. After complete denervation of the heart, they report, "there is either no change in the pulse rate (with variation of pressure), or an increase in rate with a fall in pressure, or a decrease in rate with rise in pressure." In so far as these observations testify that variations of arte-

rial pressure have *no effect* on the rate of the denervated heart, they are in accord with the earlier observations of Martin (28) and the more recent studies of Knowlton and Starling (29) who found that, between 20 and 200 mm. Hg., pressure changes did not change the rate. Frequently in the course of the work here reported arterial pressure has been raised 30 to 40 mm. Hg., after adrenal influence had been excluded, with no increase whatever in the rate of cardiac pulsation (*cf.* fig. 2). This concordant evidence wholly contradicts the first argument which Stewart and Rogoff have offered to account for the faster rate of the denervated heart when used as an indicator of adrenal secretion.

2. The second argument offered by them is that the rise of blood pressure, by increasing the rate of blood flow through the denervated heart or other organ, increases the amount of adrenin passing in unit time, and the sensitive denervated area responds to increase in the amount even if no change takes place in the rate of adrenal secretion. In presenting this argument the critics have not considered that with a rise of pressure the blood would pass more rapidly through the adrenal vessels (see p. 406); and therefore, on the basis of their own views of unvarying adrenal secretion, the higher the pressure the more diluted the adrenin—a condition which renders their argument unsound.

It is not necessary, however, to rely on argument. The simple experiment of preventing a rise of pressure may be tried. In figure 5 a record is presented of an increase in rate of the denervated heart from 144 to 180, i.e., a rise of 36 beats per minute, as a consequence of sciatic stimulation. The pressure rose about 58 mm. Hg. When the rate had fallen to 148 per minute the sciatic was again stimulated, but the pressure was prevented from rising by compression of the flexible thorax between the fingers and thumb. This is a procedure which, in the absence of the adrenal glands, is not attended by a faster beat of the denervated heart. The rate increased, however, from 148 to 184 beats per minute, a rise of 36 beats, as before. The more rapid rate developed during stimulation cannot be due to more adrenin contained in a larger volume-flow through the coronary arteries, for during stimulation the arterial pressure was not allowed to rise and augment the coronary flow. Furthermore, when the pressure was allowed to rise (50 mm.) the rapid rate, developed when the pressure was held down, did not become more rapid. The only explanation which affords a reasonable account of the faster rate is that there is something delivered to the heart through the blood stream which excites it to greater speed. Adrenin will do this. The fact that the faster rate disappears after

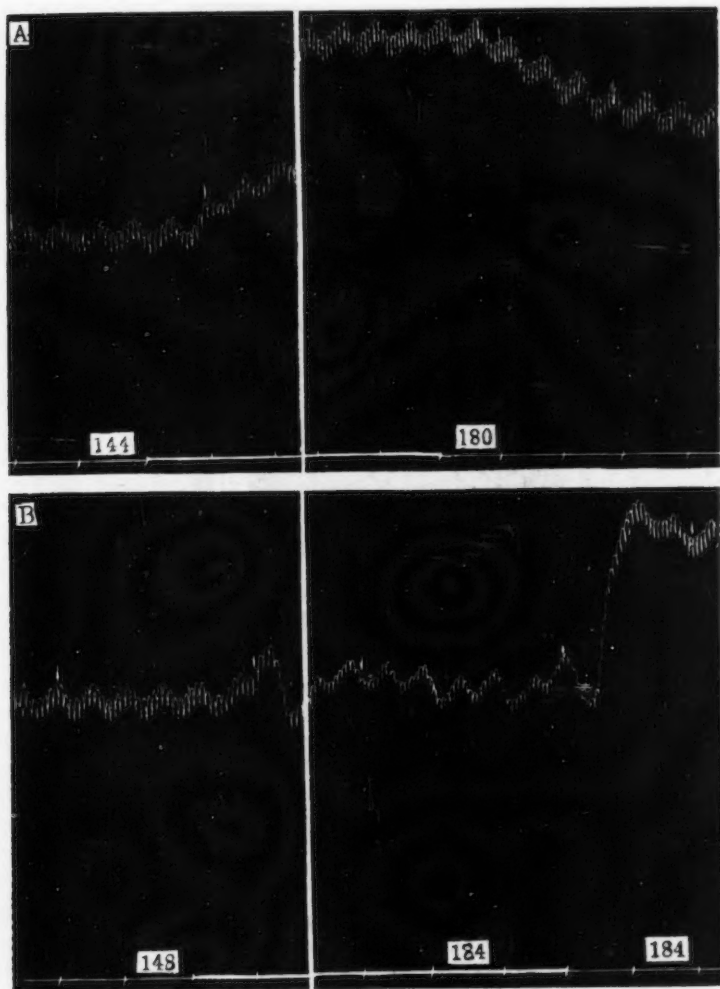


Fig. 5. Beginning and end of records of the beat of the denervated heart, mercury manometer. Original size. Time intervals, 5 seconds.

A, Sciatic stimulation 45 seconds, 1:01. Increase of rate from 144 to 180 per minute.

B, Sciatic stimulation 55 seconds (1:05). Increase of rate from 148 to 184 though pressure-rise checked by thoracic compression. No further increase with rise of pressure.

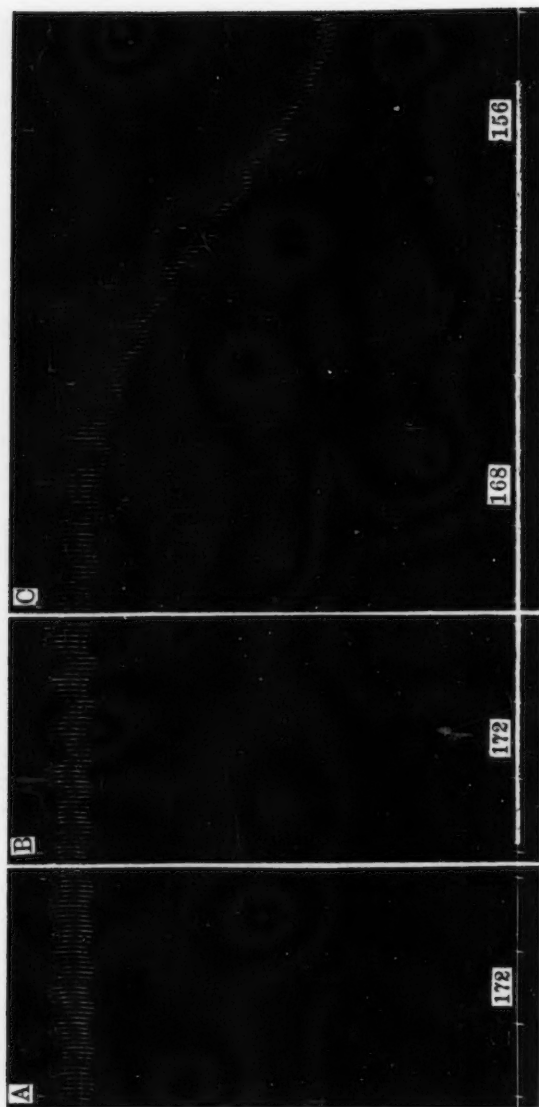


Fig. 6. Record of the beat of the denervated heart, (mercury manometer), after adrenalectomy and with a continuous uniform intravenous injection of adrenalin, 0.08 mgm. per minute. Heart rate thus increased from 132 to 172 beats per minute.

A. Time intervals, 5 seconds.

B. Beginning of 85 seconds of asphyxia. Heart rate 172 beats per minute.

C. End of 85 seconds of asphyxia. Heart rate before pressure fell, 168, later 156 beats per minute.

removal of the adrenal glands, although the rise of pressure still follows splanchnic stimulation (see fig. 1), is proof that this is the agent which is acting. Experimental test, therefore, denies the validity of Stewart and Rogoff's second argument.

3. Their third argument is directed against the use of any organ in the body as an indicator of adrenal secretion when asphyxia is employed as a stimulus, because asphyxia may be expected to alter the reactivity of the test object to adrenin, making it, for example, more sensitive. "We never supposed," they declare, "that it was possible to use in one observation an asphyxiated test object and in the comparison observation the same object with unobstructed respiration, or to assume that if there was any difference in reactions, it must be due to a difference in the rate of output of epinephrin; the condition of the test object itself being of no moment." Again this is argument and not experiment. Experiment has shown that increase of carbon dioxide causes a decrease, not an increase, in the rate of the denervated heart, and that nevertheless, adrenin, if superadded, produces a faster beat (30).

As shown in figure 6, when, after removal of the adrenal glands, adrenalin (1:200,000) is allowed to run (1 cc. in 15 seconds) steadily into a vein, asphyxia does not cause an increase of rate. The stream of adrenalin raised the rate from 132 to 172; after asphyxia had prevailed for 50 seconds the rate dropped to 168; and as the asphyxial state continued the rate became slower, dropping to 156 with a fall of pressure. A higher rate was possible, for the heart was obviously not beating at top speed, and yet there was no increase of rate at any stage in the development of asphyxia. Clearly the asphyxial condition did not render the test object more sensitive to the steady inflow of adrenalin. In the experiment illustrated in figure 2, an asphyxia lasting one minute caused an increase in the rate of the denervated heart of 32 beats a minute when the adrenal glands were connected with the circulation, but when these glands were completely tied off asphyxia for the same length of time caused no increase. The test object was in both cases subjected to identical periods of asphyxiation. Since asphyxia in the absence of the adrenal glands had no effect on the rate, whereas asphyxia with the adrenal glands present caused the characteristic acceleration which attends adrenal activity, the conclusion is warranted that the differential element in the complex, namely, the possibility of adrenal secretion, is the occasion for the typical adrenal effect. It should be remembered that Anrep (11) likewise obtained no effect of asphyxia alone,

i.e., no contraction of the denervated limb, in the absence of the adrenal glands; indeed, toward the end of the asphyxial period there was dilatation of the vessels ascribable to the direct action of the asphyxial blood on the vessel walls. This was in marked contrast to the asphyxial effect seen when the adrenal gland was present; then even a large rise of general arterial pressure, more than 50 mm. Hg., was insufficient to distend the vessels of the denervated limb, which were held contracted, according to Anrep's evidence, by secreted and circulating adrenin. Stewart and Rogoff's third argument, therefore, has no experimental warrant.

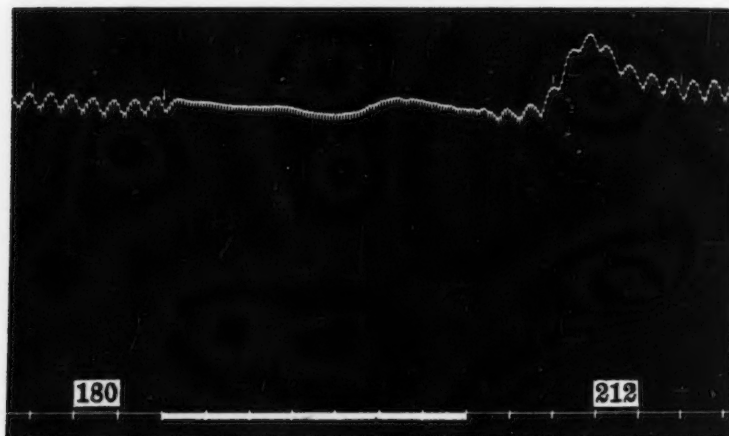


Fig. 7. Record of the beat of the denervated heart, (mercury manometer) in an animal with limb and carotid arteries tied and all mesenteric nerves severed. Enlarged one-sixth. Time intervals, 5 seconds.

Asphyxia for 35 seconds increased the heart rate from 180 to 212 beats per minute, with no noteworthy previous change in blood pressure.

4. Their fourth argument is that afferent stimulation by constricting the splanchnic vessels lessens the blood flow through the liver; in consequence the adrenal secretion contained in the cava blood is less diluted (i.e., more concentrated) than normal and therefore has more stimulating power. Again it is not necessary to rely on argument. In figure 7 is presented a record of the beats of a denervated heart in an animal in which all the nerves of the mesentery were entirely severed and the animal then asphyxiated. The rate before asphyxia was 180

beats per minute. This was increased by asphyxia 32 beats per minute. There is no possibility under these circumstances of any greater concentration of secreted adrenin because of failure of blood to pass through a constricted splanchnic area, for the nerves which would cause constriction of these vessels had been previously cut. Furthermore, the pressure did not fall, i.e., the flow was not made slower during the asphyxiated period. The effect must be ascribed to greater concentration of adrenin in blood delivered to the heart, due to an increased secretion of the adrenal medulla. The fourth argument, therefore, like the first three, fails to stand experimental test.

An observation having an important bearing on all four arguments and, indeed, on all conclusions arising from use of the "cava pocket" is that reported above (see p. 415) in giving evidence of adrenal activity at times of emotional excitement. As figure 4 shows, the rate of the denervated heart in an animal resting quietly with the adrenal glands intact was 217 beats a minute. When these glands were removed, *there was not at any time a reduction of the rate*. Recently Stewart and Rogoff (30) have testified that the "steady spontaneous discharge" from the adrenal glands in their experiments—an amount estimated as not more than 0.0002 mgm. per k. per minute—is sufficient to affect the heart. If with nerves intact there were in natural conditions the constant secretion which they declare to be "normal," removal of the glands should have been followed by a slower pulse. That the pulse did not fall below the "quiet" rate after adrenalectomy obviously permits the inference that in calm and peaceful existence there is no secretion from the adrenal glands sufficient to influence the response of an extremely sensitive indicator. In that case any attempt to explain the increased heart rate by greater delivery of adrenin or by greater concentration of it in the blood, due solely to shifts of the circulation, would be not at all pertinent.

The only factor which Knowlton and Starling found effective in causing prompt alteration of rate of the isolated heart was change of temperature. In order to increase the rate 40 beats per minute, however, the temperature of blood entering the heart had to be raised about 7°C. (29). It is inconceivable that the effects recorded above are due to the delivery of warmer blood to the heart.

From the foregoing facts the conclusion is warranted that the explanations offered by Stewart and Rogoff to account for adrenal effects on the basis of greater flow or altered distribution of the blood have no experimental support.

CRITICISM OF METHODS YIELDING NEGATIVE EVIDENCE

A review of the previous sections of this paper reveals unanimous agreement among investigators, with the exception of Stewart and Rogoff, that painful stimulation, asphyxia and emotional excitement evoke adrenal secretion. Nevertheless, the care with which Stewart and Rogoff conducted their experiments, the quantitative methods which they employed and the variety of their experiments have led to their results being given a considerable degree of credence. As previously stated, the discrepancy between their conclusions and those reached by all other investigators naturally raises the question as to whether some difference in the methods employed would not account for the difference in the results. Since Stewart and Rogoff are alone in their contentions, it is perhaps reasonable to inquire whether the peculiar method which they employed, rather than the various methods used by others, may not have features which would account for the discrepant results.

The method of Stewart and Rogoff. Stewart and Rogoff obtained evidence of adrenal secretion by the use of a "pocket" in the inferior vena cava (32). This pocket was made by clamping the vena cava immediately above the iliacs, then clamping the renal veins, emptying the cava segment by stripping it upwards, and placing a clamp on the vessel above the entrance of the lumbo-adrenal veins. Any small branches of the cava segment were tied. The pocket thus formed was allowed to fill with blood from the adrenal veins, and the blood was either allowed to pass into the general circulation by removal of the clamp on the inferior cava, or was withdrawn and tested outside the body on preparations of rabbit uterus and intestine. The arrangement was modified in the "permanent pocket" by tying splanchnic vessels and shutting off the blood flow in the hind quarters. Experiments performed under these conditions revealed a spontaneous liberation of adrenin.

In one of their early papers Stewart and Rogoff state (32) that they are "not able to decide definitely whether this liberation is a normal physiological process merely unveiled by the experiments, or an abnormal process dependent upon the necessary conditions of the observations,—anesthesia, unavoidable excitation of afferent nerves, etc." They mention, however, the relative constancy of the amount secreted as in favor of the former hypothesis. Later they suggest that the extensive operation required by their procedure may have produced so

great a spontaneous discharge that no detectable increase could be produced, and they admit that Tschoboksaroff's failure to obtain increased adrenal secretion on sensory stimulation may have been due to the severe operative procedure which he employed (33). This earlier caution regarding their method they seem to have gradually abandoned, for later they mention (7) the spontaneous secretion as being the "normal output of epinephrin" and state (34) that after section of the spinal cord the secretion has all the characters of "normal secretion," and they repeatedly allude (9) to the amounts of adrenin found in the pocket as being the normal amounts. In recent papers (27), (35) they refer to their results as constituting "a striking illustration of the fact dwelt upon in previous papers that the output of epinephrin is relatively stable and not easily influenced experimentally," and they speak of the secretion occurring at a relatively constant rate as the "naturally secreted epinephrin of the organism." Rogoff (36) goes so far as to declare "it has been established beyond doubt that the adrenal glands continuously secrete a certain normal amount of epinephrin."

Before this view can be admitted, the effect of opening the abdominal cavity, clamping off the inferior cava, and repeatedly manipulating the abdominal contents, either in pressing blood out of the inferior cava or withdrawing it by syringe, must be examined. Fully twenty years ago Bayliss and Starling called attention to the profound effect which opening the abdominal cavity has on the intestines in causing them to become absolutely motionless. Local stimulation then provokes no response or only local contraction. *If both splanchnic nerves are divided*, the intestines within a short time commence to contract rhythmically and show the usual local reflexes. In order to study intestinal movements with the abdomen opened, they had to section both splanchnic nerves, or destroy the spinal cord, or excise the abdominal ganglia. "These facts," they state (37), "suggest that in the intact animal, at any rate under the conditions of our experiment, tonic or reflex influences are continually descending the splanchnic nerves and inhibiting the activity of the intestines." The observations of Bayliss and Starling may be confirmed by any one who will study gastrointestinal movements in the opened abdomen. Even if there is slight indication of activity at any time with the splanchnics intact, the least stimulation applied to the intestine, even a gentle handling of the gut, suffices to produce a reflex inhibition of its entire extent. These well-established facts make an interesting commentary on the use of the

cava pocket as a mode of obtaining evidence of "normal" or "natural" secretion. There is no doubt that secretion from the adrenal medulla is subject to impulses delivered by the splanchnic nerves, and there is no doubt that opening the abdominal cavity under anesthesia results in a discharge of impulses along these nerves. The adrenal glands, therefore, are continuously and abnormally stimulated if the abdomen is opened. The conclusion that must be drawn is that the pocket method is incapable of yielding any reliable evidence regarding the "normal" secretion of these glands.

The isolated heart yields pertinent testimony as to the discharge of impulses along splanchnic pathways under experimental conditions. An examination of the cases summarized in tables 1 and 2 reveals that, after section of the splanchnic nerves or exclusion of the adrenal glands, there is a drop in the heart rate—in some instances 40, 44 and even 48 beats per minute. The most reasonable explanation for this result is that in these experiments splanchnic impulses were continuously stimulating the glands to activity and thus making the heart beat faster than it otherwise would. Quite apart from these effects, evidence exists in the inhibitory influence of anesthesia on gastrointestinal movements that anesthesia alone can arouse splanchnic impulses (*cf.* also Elliott, *loc. cit.*). Thus the "steady spontaneous discharge" from the adrenal glands, described by Stewart and Rogoff as "normal," is confirmed and explained. But one needs only to compare the drop in heart rate after adrenalectomy in acute experimental conditions (see figs. 1 and 2) with the absence of a drop after adrenalectomy in the non-anesthetized animal (see fig. 4) to realize how abnormal is the so-called "normal" secretion which occurs during operation.

Stewart and Rogoff, after considering the possibility that their "extensive operation" may have caused so great a secretion of the adrenal glands that asphyxia, for example, could not evoke a detectable increase, became convinced that this suspicion was not well founded because they noted, on stimulating the cut splanchnic nerve directly, evidence of a decidedly greater rate of secretion (38). Obviously, when a nerve is cut and then stimulated, an unusual effect may be due to liberation of material accumulated during the inactivity which followed denervation. Furthermore, because direct stimulation of a nerve, or central excitation by strychnine, will produce certain results, that is not proof that reflex stimulation, done under anesthesia, should produce the same results. For example, there is a marked difference between the intensity of muscular response caused by direct stimulation of the

sciatic nerve and that which may be induced by reflex stimulation. Again, an abdominal operation which arouses continuous activity in the splanchnic nerves might readily interfere with splanchnic reflexes. One of the methods employed by Cannon for recording graphically the effect of secreted adrenin in the body was that of denervating the mesentery, as described above (see p. 410). This method required opening the abdomen. It yielded constant results so far as the belated influence of asphyxia was concerned, but was commonly disappointing as a means of demonstrating the early influence of asphyxia; *and in the entire series of cases with opened abdomen there was only one in which sensory stimulation caused any effect ascribable to adrenal secretion.* For example, in the first five cases of table 2, the abdomen had been opened, and in these instances, though asphyxia was effective, sciatic stimulation yielded no response whatever. From this evidence it is clear that, either because the opening of the abdomen produces a secretion unsurpassable by reflex stimulation, or because that operation abolishes abdominal reflexes, the influence of sensory stimulation on the adrenal glands is not manifested. There is little wonder, therefore, that Stewart and Rogoff, who alone have employed the pocket method, with its attendant severe abdominal operation and repeated manipulation of the abdominal contents, failed to obtain the positive results which have been obtained by all other observers.

The foregoing facts and considerations warrant the conclusion that although the work of Stewart and Rogoff was admirably quantitative in character, it was done under experimental conditions which could not afford information regarding the normal secretion of the adrenal glands or the natural conditions which affect that secretion. This conclusion applies to all inferences as to the nature of adrenal activity which they have based upon employment of the pocket method.

The method of Gley and Quinquaud. In the paper by Gley and Quinquaud previously mentioned (10), evidence is adduced to prove that adrenal secretion has nothing to do with the efficacy of sympathetic nervous impulses as they affect the smooth muscles of blood vessels, a conclusion well supported by the previous observations of Hoskins and McClure (39). Gley and Quinquaud removed blood from the inferior cava immediately above the opening of the subhepatic veins, and again from the right or left ventricle, in each case after splanchnic stimulation. The blood thus obtained was injected in 20 cc. amounts into other dogs weighing from 4 to nearly 10 kilos. Only the blood which was taken from directly above the opening of the

adrenal veins caused any rise of pressure in the dog injected. They conclude, therefore, that the adrenin present in adrenal blood after splanchnic stimulation is found neither in the blood of the vena cava above the subhepatic veins nor in the blood of the heart.

In drawing this conclusion Gley and Quinquaud seem to have disregarded the fact that they were, in the first place, taking only a small portion of the secreted adrenin, which had already been diluted by the blood of the donor, and were then injecting this small portion into the blood stream of another dog, where it would be diluted to a much greater degree.

Gley and Quinquaud declare categorically that secreted adrenin is not carried by the circulation to the organs on which it acts, and that, if present at all, it is present in a quantity altogether minimal and insufficient to exercise its action. This declaration again is made without due regard to evidence already in the literature. The observations on the denervated limb, on the denervated kidney, on the denervated salivary gland and on the denervated heart, quoted or described above, clearly demonstrate that adrenal secretion may be stimulated by painful impulses, by asphyxia and by emotional excitement, and that the substance secreted under these circumstances not only is carried to the structures on which it acts, but produces on these structures pronounced physiological effects. Until this evidence is definitely proved to be unworthy of acceptance, the conclusion which Gley and Quinquaud have drawn must be regarded as quite unjustified.

INTERPRETATION OF THE FUNCTION OF THE ADRENAL MEDULLA

With the disappearance of the view that the adrenal glands produce some substance which neutralizes toxic material developed in the body, there have been left two theories to account for the rôle played by the adrenal medulla in the bodily economy. These are the tonus theory and the emergency theory.

The tonus theory, which has been advocated in the past (40) and still receives attention, holds that the function of the secreted adrenin is to maintain the sympathetic endings in a state of responsiveness to nervous stimulation or in a condition of moderate activity or tone. This view has definitely lost ground in the course of relatively recent investigations. A number of investigators have called attention to the depressive effect of small doses of adrenalin (39), (41). If the smallest dose which will have any influence whatever on the blood

vessels induces relaxation of the vessels, it is difficult to understand how the function of the secreted adrenin could be that of maintaining a state of tonic contraction. Furthermore, as has been repeatedly noted (42), double adrenalectomy does not for some time cause the fall of arterial pressure which naturally would be expected if continued adrenin secretion were needed to keep the pressure up; and also stimulation of the splanchnic nerves induces the same rise of pressure after adrenalectomy as before (10). From these results the conclusion has been drawn by Hoskins and McClure and by Gley and Quinquaud that the tonus theory is without adequate experimental support.

The emergency theory was presented by Cannon on the basis of studies of adrenal secretion following stimulation of afferent nerves, asphyxia and emotional excitement. In the papers bearing upon this theory emphasis was repeatedly laid upon the association between adrenal activity and the activity of the sympathetic division of the autonomic system in such emergencies. Nowhere has the statement been made that secreted adrenin has a function separate from that of the nerve impulses, except to increase the irritability of fatigued muscles (3) and to speed the coagulation of the blood (4). The idea originally suggesting these studies on adrenal secretion was that changes in the viscera originally induced by nervous impulses might be continued by circulating adrenin (43, p. 40). No claim has ever been made that there is at any stage a primacy of adrenin in the production of physiological or psychological changes seen during strong emotion.

In spite of the foregoing facts authors have written as if Cannon had been attempting to support the idea that emotional experiences were dependent upon circulating adrenin. Thus Stewart and Rogoff report (32), as if the matter had been questioned, that all signs of fright can be elicited by administering morphine to a cat with one adrenal removed and the other denervated.⁶ Rogoff points out (36) that the secretion of sufficient adrenin to produce symptoms of fright would be impossible, again as if any claim had been made that these symptoms were due to secreted adrenin. Gley and Quinquaud declare that the

⁶ Stewart and Rogoff noted dilatation of the pupil of the "denervated eye" when animals became frightened, though one adrenal was removed and the nerves to the other sectioned. Cannon and de la Paz tried this method of testing for adrenal secretion but could not persuade themselves that an eye still innervated by the third cranial nerve was really "denervated" and interpreted the prompt dilatation of the pupil in a paroxysm of rage as due to central inhibition of the still active constrictor muscles (see Cannon: *Bodily Changes in Pain, Hunger, Fear and Rage*, New York, 1915, p. 35).

persistent irritability of the nerves after the adrenal glands have been removed is opposed to the explanation which Cannon has given to experiments on the adrenin origin of emotions (10). Indeed, Cannon has been definitely charged with assuming that the reaction to fear and other emotional states is dependent on hypersecretion of adrenin (44). Careful reading of his work gives no support for these interpretations.

The concept of an emotion may be expressed either in psychological terms of subjective experience or in physiological terms of bodily change. Cannon's observations lend no support to the idea that adrenal secretion is essential to the subjective experience of strong emotion. Adrenin has its effect peripherally, on outlying viscera. An assumption that subjective feeling depends on circulating adrenin involves, therefore, supporting the view that emotion as a psychological state is the consequence of visceral changes. Cannon has, in fact, definitely argued against this view (43, p. 275).

If the critics of the emergency theory conceive emotion as bodily change, they will find in Cannon's consideration of the interrelations of emotions the point emphasized that it is the *sympathetic division of the autonomic system* which is the primary agency in mobilizing the bodily forces in times of great fear or rage (43, p. 268). To assume that secreted adrenin is necessary for the changes which occur under such conditions implies an acceptance of the tonus theory. This view has not been held by Cannon and receives no support in any observation he has reported. The only suggestion which he has offered (43, p. 64) that might be construed into support of such a view is that adrenal secretion given forth into the blood stream during excitement is a substance capable of inducing or augmenting the nervous influences which bring about the very changes in the viscera that accompany excitement. Naturally, this suggestion should be considered in conjunction with others; e.g., "it is possible that disturbances in the realm of the sympathetic are automatically augmented and prolonged through chemical effects of the adrenal secretion" (43, p. 38), and "the changes originally induced in the digestive organs by nervous impulses might be continued by circulating adrenin" (43, p. 40). These suggestions imply coöperation of chemical and nervous factors, but not a dependence of the nervous factors on the chemical.

The possibility has been recognized (43, p. 65) that in times of emotional stress there may be coöperation of secreted adrenin with the products of other endocrine glands simultaneously excited, which might render the adrenin much more effective than it would be by itself.

This is a possibility which should be kept in mind in connection with the emergency theory of adrenal secretion. Until this possibility has been tested, however, there is no need of going further than the facts will warrant in appreciating the coöperative character of secreted adrenin and sympathetic nervous impulses.

Thus far no reliable evidence has been brought out by any investigator that there is any secretion whatever of the adrenal glands under quiet, peaceful conditions. Results reported in this paper present the first indication that under such conditions there is no adrenal secretion or a secretion so slight as not to affect the denervated heart, an extremely sensitive indicator. Stewart and Rogoff have shown that the cat and the dog will live normally for weeks with one adrenal excised and the other denervated, an operation which results in no demonstrable flow of adrenin from the adrenal vein (45). These observations prove that adrenal secretion is not a necessity, at least in times of serene existence. Adrenin is secreted, however, in times of great emotional stress and under circumstances which cause pain or asphyxia. As stated at the beginning, the function of the adrenal medulla is to be looked for under conditions which rouse it to action. Excitement, pain or asphyxia are, in natural existence, commonly associated with violent struggle for self-preservation. Under such circumstances, as has been emphasized in the presentation of the emergency theory, the operation of the sympathetic division of the autonomic system together with the aid which adrenin affords will muster the resources of the organism in such a way as to be of greatest service to such organs as are absolutely essential for combat, flight or pursuit. It appears, therefore, that the emergency theory of the adrenal medulla is the only one which thus far has any experimental support.

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EFFECT OF WORK AND HEAT ON THE HYDROGEN ION CONCENTRATION OF THE SWEAT

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INTRODUCTION

Early in the year 1918 my attention was attracted to some work that had been done several years ago demonstrating, incidentally, how muscular fatigue might affect the reaction of the urine. The fact that the results were conflicting, and particularly that all the investigators used methods of titration, which we now recognize as quite unreliable for obtaining total acidity, led me to think that this might prove an interesting field for research. Furthermore, inasmuch as the literature seemed to be silent as to whether exercise in any way affected the reaction of the sweat, it seemed to be desirable to make determinations on the urine and sweat simultaneously, with the subject under the same conditions, with the view first, of establishing more definitely the results of the earlier observers as far as the urine was concerned; second, to ascertain if any reaction changes occur in the perspiration; and third, whether these changes, if they occur, show either a supplementary or a compensatory relationship with the urine.

With these ideas in mind I made a few preliminary tests in Ripon College chemical laboratory through the courtesy of Dean Barber and Professor Barker. However, the problem was not attacked in an intensive manner until I had the privilege of pursuing the work during the school year of 1918-1919 in the physiological laboratory of Professor Howell in the School of Hygiene and Public Health of the Johns Hopkins University. It therefore seems most fitting that I should here acknowledge my deep gratitude to him for his helpful suggestions and above all the inspiration that I received from his kindly interest. In the same manner I wish to thank Doctor Spaeth of this laboratory for assistance with the experimental technique.

It is my purpose in this article to consider simply the perspiration, and to discuss subsequently the results obtained from the urine.

We have in the past been quite willing to assume that the principal function of the sweat glands is for the regulation of body temperature, and not much emphasis has been laid upon the significance of the composition of the excretion.

Before entering upon the discussion of the problem some of the views that have been held in the past as to the reaction of the sweat, more or less conflicting, may be stated briefly.

Foster (1) states that "Sweat from a well washed skin is alkaline. It is only when mixed with sebum that it is acid. Horses' sweat is said to be always acid." Smith (2) finds horses' sweat strongly alkaline. Moriggia (3) states that in herbivora the reaction is generally alkaline, while in carnivora it is acid. Gaube (4) speaks of the human sweat as acid, while that of the horse, cow, dog, cat and hog is alkaline. Certainly omnivora, herbivora and carnivora are found in this last list. In Landois' text (5) we find the statement that "swine sweat (?) on the snout, cattle about the mouth (?), while goats, rabbits, rats, mice and dogs do not sweat at all." Aron has stated that monkeys have no sweat glands but Shaklee (20) in later work reports that this is an error, "the skin seems everywhere provided with well-developed sweat glands."

METHODS

As has been suggested above, the criticism that may be made upon earlier work is concerned with the uncertainty of the data obtained by titration. In the observations which follow, use was made of the colorimetric and the gas chain methods in order to obtain the total acidity. As to the former, I followed mainly the method of Henderson and Palmer (6), which is an adaptation of the Sørensen method, while for the gas chain measurement I used a Leeds and Northrop's potentiometer with Clark's (7) hydrogen electrode shaker. It was hardly thought necessary to use a constant temperature chamber, but a thermometer was kept in the potassium chlorid vessel and therewith the corrections were made.

For the colorimetric method it may be stated briefly that there are required five standard solutions made up of monopotassium phosphate and disodium phosphate, mixed in such proportions that each solution will possess a distinct and definite pH value. In like manner, acetic acid and sodium acetate are so mixed as to give six standard solutions of

definite pH values. The former mixture is for use on the alkaline side with values ranging from 8.7 pH to about 7.0 pH. The latter reaches from 7.0 pH to 4.7 pH. These standards are as a rule made fresh once a week, but never kept longer than two weeks. When ready for tests, 4 cc. of each standard was taken and diluted with distilled water up to the mark in a 100 cc. flask, and a similar dilution was taken for the sweat. An equal amount of indicator added to the same volume of the diluted standard and the diluted sweat and the colors thereby matched gave a fair evaluation for the reaction of the latter even where interpolation was necessary.

As to the indicators, phenolphthalein can be used for values between 8.7 pH and 8.0 pH. Neutral red, however, is very useful between 8.0 pH to even below the neutral point 7.0 pH. Methyl red is excellent on the acid side from 5.7 pH to 4.7 pH, and is not affected by proteins, while p-nitrophenol covers a wider range and is an excellent indicator between 6.7 pH and 4.7 pH. Sodium alizarine sulphonate covers the entire field from 8.0 pH to 4.7 pH, thereby meeting all of the variations that I have found in the perspiration. There were, at times, in use the indicators that are recommended by Clark and Lubs (8), which were quite satisfactory.

In the main the determinations were made by the colorimetric method, while the potentiometer was used for checking up the standard solutions.

Unfortunately the gas chain was not brought into use as often as one might wish, because at times tedious delays were caused by not being able to get the services of a mechanician.

I am aware that objections may be urged against placing too much reliance upon absolute evaluation by the colorimetric method. "Off-shades" did arise at times, especially with the use of sodium alizarine sulphonate. In that case determinations had to be made with other indicators or the test would have to be rejected.

The protein and salt errors have been long recognized by Sørensen and others. As to the former, I have a feeling that the per cent in the sweat is so low that its effects are quite negligible. As to the latter, I have not that same confidence, for the work of Viale (9) shows variations in the salt content. Of late some have laid considerable emphasis upon the variations due to the carbon dioxid factor.

However, after making due allowance for these liabilities to error it must not be overlooked that Lubs and Clark (10) and others have obtained some remarkable agreements in the two methods.

Granting that there might be some slight errors in the absolute, there can hardly be any errors in the relative values, as the samples to be compared were tested almost simultaneously.

My first tests were made on volunteers from the Baltimore Central Y. M. C. A. and upon a few of the workmen about the laboratory. These were hardly more than preliminary try-outs, as was ultimately proven. In some cases the skin was cleansed with water or alcohol, while in others not at all. The samples which were collected at the Y. M. C. A. were really the combination effect of heat and work, for the subjects, after playing basket-ball or volley-ball, as the case might be, came into the hot-room where the samples were obtained.

One important point revealed by these tests was that the sweat contains a greater concentration of hydrogen ions than one would naturally suppose.

However, the futility of the volunteer plan soon became apparent. It was evident that in order to make the experiments worth while it was necessary to have reliable and well selected subjects who would be willing to come to the laboratory, where it would be possible to have better controls. This end was realized by obtaining as subjects some medical students, who had a much better appreciation of the importance of the work and were willing to coöperate in a most excellent manner.

The few subjects that I used, mainly, were in perfect health, as they had passed the tests as donors of blood for transfusion cases. After undertaking the work in the laboratory my first thought was to ascertain if exercise produced any changes in the hydrogen ion concentration of the sweat. Consequently there arose the suggestion of a control.

My idea was to obtain heat-sweat first and then secure work-sweat immediately afterwards, with the feeling that if any change took place in the latter it would be as in the case of the urine in the elimination of more acid as a result of work.

The subjects were stripped and the parts from which the sweat was to be taken, viz., face, chest and abdomen, were first washed with soap followed by cleansing with water, ether and alcohol in the order named. In the application of the last two liquids dental napkins were used. The subjects were then placed in a hospital sweat-cabinet with a fair amount of moisture, starting with a temperature of about 30°C. and finally increasing it to 40° or 45°C. The heating lasted from fifteen to twenty-five minutes, according to the subject and the number of samples to be obtained. All samples of sweat were collected by means of lipless specimen tubes.

After this procedure, the parts being controlled as before, the subject was placed on a stationary bicycle where he worked for fifteen to twenty-five minutes. The samples of work-sweat and heat-sweat were then tested as soon as possible and comparisons were made.

The most striking thing about the data, in the securing of which there were sixteen observations upon six different individuals, was that in each instance the heat-sweat was of a greater hydrogen ion concentration than the work-sweat. (See table 1, series A.)

TABLE 1

HEAT PRECEDING WORK SERIES A				WORK PRECEDING HEAT SERIES B			
Subjects	pH heat-sweat	pH work-sweat	Difference	Subjects	pH work-sweat	pH heat-sweat	Difference
G.	5.4	5.9	0.5	G.	5.8	5.4	0.4
G.	5.5	5.65	0.15	G.	5.8	5.5	0.3
G.	5.25	5.8	0.55	G.	5.7	5.5	0.2
J.	5.8	6.4	0.4	G.	5.9	5.2	0.7
J.	6.4	6.6	0.2	G.	5.9	5.15	0.75
J.	5.4	7.0	1.6	J.	5.6	5.6	0.0
E.	7.2	7.5	0.3	J.	6.1	5.5	0.6
E.	7.1	7.4	0.3	E.	7.4	5.3	2.1
E.	6.0	7.4	1.4	F.	5.8	5.2	0.6
E.	5.6	7.4	1.8	C.	5.45	4.7	0.75
E.	5.7	6.5	0.8	S.	6.15	5.5	0.65
E.	5.7	6.5	0.8				
E.	5.6	6.8	1.2	6	5.96	5.32	Av. dif. 0.64
B.	6.2	7.4	1.2				
A.	5.6	6.0	0.4				
M.	5.1	5.9	0.8				
6	5.22	6.63	Av. dif. 1.41				

Fearing that the first excretions might be more acid due to the sebum or other causes, I reversed the process by producing work-sweat first. I made eleven observations with the use of six individuals, with the result that the heat-sweat was still of higher acidity. (Note table 1, series B.)

I next adopted the plan for a few experiments upon subject G. of producing sweat in the morning by work and by heat in the afternoon, and then reversed this process, with no particular differences in the results.

All of the remainder of the experiments were performed on two individuals simultaneously, one producing heat-sweat and the other work-

TABLE 2

TESTS	SUBJECTS	pH WORK	pH HEAT	AVERAGE DIFFER- ENCE	TESTS	SUBJECTS	pH WORK	pH HEAT	AVERAGE DIFFER- ENCE
1	G.	5.9	5.5		1	E.	7.5	7.2	
2	G.	5.65	5.4		2	E.	7.4	7.1	
3	G.	5.8	5.25		3	E.	7.5	7.2	
4	G.	5.8	5.5		4	E.	7.4	7.1	
5	G.	5.7	5.2		5	E.	7.4	6.0	
6	G.	5.9	5.0		6	E.	6.5	5.6	
7	G.	5.8	5.25		7	E.	6.5	5.7	
8	G.	5.7	5.5		8	E.	6.8	5.7	
9	G.	5.6	5.4		9	E.	7.4	5.6	
10	G.	5.8	5.4		10	E.		5.8	
11	G.	5.8	5.4		11	E.		5.3	
12	G.	6.0	5.85				7.15	6.24	0.91
13	G.	5.6	5.6						
14	G.	5.6	5.6						
15	G.	5.8	5.4						
16	G.	5.8			1	J.	6.4	5.8	
17	G.	5.7			2	J.	6.6	6.4	
18	G.	5.35			3	J.	5.6	5.4	
19	G.	5.35			4	J.	6.1	6.4	
20	G.	5.9			5	J.		5.8	
					6	J.		5.2	
		5.73	5.42	0.31			6.18	5.83	0.35
1	M.	5.1	5.1						
2	M.	5.4	5.4						
3	M.	5.95	5.85						
4	M.	5.65	5.6						
5	M.	5.8	5.6						
6	M.	5.8	5.4						
7	M.	6.4	5.8						
		5.84	5.54	0.30					

TABLE 3

OBSERVATION	SUBJECTS	pH WORK	OBSERVATION	SUBJECTS	pH HEAT
20	G.	5.73	15	G.	5.42
7	M.	5.84	7	M.	5.54
9	E.	7.15	11	E.	6.24
4	J.	6.18	6	J.	5.83
13	X.	6.19	14	X.	5.61
Total 53		Av. 6.22	Total 53		Av. 5.73

TABLE 4

SERIES A HEAT-SWEAT pH				SERIES B WORK-SWEAT pH		
Subjects	First sample	Second sample	Third sample	Subjects	First sample	Second sample
G.	5.5	5.6		G.	5.7	5.8
G.	5.5	5.65		G.	5.6	5.65
G.	5.2	5.45		G.	5.8	5.9
G.	5.12	5.2		G.	6.0	5.8
G.	5.0	5.2		G.	5.6	5.55
G.	5.25	5.3	5.5	G.	5.8	5.6
G.	5.5	5.55	5.6	G.	5.7	5.9
G.	5.4	5.55	5.55	G.	5.9	5.8
G.	5.85	5.15		G.	5.35	5.3
G.	5.6	5.45		G.	5.7	5.75
G.	5.6	5.3		G.	5.9	5.95
G.	5.4	5.45		G.	5.9	5.6
G.	5.4	5.5		G.	5.65	5.7
G.	5.5	5.6		G.	5.8	5.75
G.	5.25	5.2				
M.	5.4	5.15	5.5	M.	5.5	5.8
M.	8.0*	5.2	5.25	M.	5.95	5.15
M.	5.85	5.8		M.	5.65	5.9
M.	5.6	5.35		M.	5.8	5.85
M.	5.4	5.25		M.	5.8	5.4
M.	5.8	5.6	5.8	M.	6.4	6.3
M.	5.1	5.2	5.4	M.	5.9	5.8
				M.	5.8	6.0
E.	5.9	5.7				
E.	5.4	5.25				
F.	4.85	4.7	5.1			
S.	5.35	5.7	5.8			
J.	5.2	5.35	5.3			
O.	5.9	5.7				

* This unusual reading may be due to the fact that the subject had served as a donor in a blood transfusion three hours before the experiment.

sweat, while the next day the performance was reversed. The grand totals from these experiments are given for four of the subjects in table 2.

Table 3 gives averages of the four principal subjects, while X. represents the average of several individuals taken together where not more than one or two tests were made on each person.

In table 4, series A, are found twenty-eight experiments in which two samples of heat-sweat were taken, while in series B of the same table we have twenty-two experiments in which two samples of work-sweat were taken. It is a remarkable coincidence that just 50 per cent of the second samples increased in acidity in both kinds of experiments.

There were ten tests in which three samples were taken successively as a result of heat. Comparing the third with the first sample we now find that eight are less acid, while one is more acid and one remains the same. In comparing the third with the second sample we again find that eight are less acid, one is more so, while one remains the same. The skin was cleansed as before after each collection, and an interval of five minutes elapsed between the collection of the successive samples.

CONCLUSIONS

In my conclusions I wish to emphasize that in many cases the changes were exceedingly small, yet the distinction was always obvious. Furthermore it is to be remembered that the work experiments were not long-enduring and fatiguing tests like those that have been reported in the past on the urine. On the contrary the subjects as a rule had performed their part of the experiments within one hour. While the time was short, the experiments, especially from exercise, were rather intense. In a majority of cases these tests took place late in the forenoon, ranging from two to five hours after a meal.

The work reveals the following facts:

First, that sweat caused from either work or heat is acid, probably always so in perfect health, and the degree of acidity is greater than we have heretofore believed.

Second, in a continued secretion of sweat the reaction does not remain entirely constant. A second sample may show a slight increase or decrease in acidity, while a third sample shows practically in all cases a small but distinct diminution compared with the first sample.

Third, the sweat caused by external heat is always more acid than that caused by muscular work.

Many authors have assumed that the secretion of sweat is normally alkaline and that the acid reaction actually shown in many cases is due to admixture with sebaceous secretion. But Francois-Franck (11), Kittsteiner (12) and others, state that the sweat from the palm of the hand is acid, although this portion of the skin is devoid of sebaceous glands. The observations reported in this paper also throw doubt upon this explanation of the acidity of sweat as usually collected, since the precautions taken to cleanse the skin before collecting the sample should have been sufficient to remove any deposit of sebaceous material. The immediate cause of the acidity of sweat has not been determined satisfactorily. Halliburton (13) states that the sweat, like the urine, contains acid phosphates, but this explanation has not been corroborated by satisfactory analyses. Others have assumed the presence of volatile fatty acids in the secretion, and some observations of my own tend to support this view. In a number of cases the insensible perspiration was collected by fixing a finger suitably in a glass chamber, so that the vapor would condense upon the walls of the vessel. When diluted and compared with distilled water this condensate gave always an acid reaction. Aubert (14), Röhlhig (15), Schierbeck (16), Fubini and Ronchi (17), have emphasized the importance of carbon dioxide. The amount of carbon dioxide excreted varies with exercise and especially with external temperature. Schierbeck, for example, found that at a temperature of 29.8°C. there was an elimination of 8.9 grams of carbon dioxide in twenty-four hours, while at a temperature of 38.4°C. the amount excreted in the same period was 29.5 grams. The larger excretion of carbon dioxide would increase the acidity of the sweat as secreted, but presumably this factor did not enter into the reactions as determined by the method described in this paper. In these determinations the diluted specimens were exposed freely to atmospheric air, and presumably took on a corresponding tension of carbon dioxide.

The statement of Heuss (19), "Der schweiss reagirt in der Ruhe normaler weise sauer bei profuser secretion (Pilocarpin, Schwitzbäder) kann er neutral ja sogar alkalisch werden," I could hardly support unreservedly. So far I have not tested any sweat produced by drugs, so I have nothing to offer on that point. However, when I have followed work with heat I have found that the sweat from the latter is not only more acid, but more profuse.

So the question of the profuseness, so often referred to in the literature, does not in itself offer a satisfactory explanation of differences in reaction.

The fact that heat-sweat shows uniformly a higher hydrogen ion concentration than work-sweat is surprising and contrary to expectation. In muscular work there is a large increase in the acid products of metabolism, and the output of acid in the sweat can be understood as part of the mechanism for preserving the acid-base equilibrium of the body. In heat-sweat we have heretofore regarded the secretion and evaporation of the water as an important means of controlling the body-temperature, the so-called physical regulation of the heat-equilibrium of the body. The fact that this heat-sweat is acid may be looked upon as a demonstration that the sweat in man under ordinary dietary conditions is normally acid, and that this secretion, like that of the urine, helps to maintain the acid-base equilibrium of the organism. But why the heat-sweat should exhibit a greater acidity than the work-sweat is not clear. It is hoped that further study of this problem may prove not only of physiological, but of therapeutical value.

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EFFECT OF PHYSICAL TRAINING AND PRACTICE ON THE PULSE RATE AND BLOOD PRESSURES DURING ACTIVITY AND DURING REST, WITH A NOTE ON CERTAIN ACUTE INFECTIONS AND ON THE DISTRESS RESULTING FROM EXERCISE¹

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INTRODUCTION

There are two methods of conducting an inquiry into the effects of physical exercise. On the one hand one may make a study of a very large number of subjects and average the results. The objection to this method is that it assumes that the numerous irrelevant variables, of which no account is taken, cancel one another so that the result indicates the action of a single common factor (exercise) and of its variations. On the other hand one may make an intensive study of a very few subjects. The objection here is that we are prone to assume that what is true of these few subjects is true of all potential subjects, whereas the cases studied may be exceptional ones.

To those who do not forget the limitations of these methods both are useful, suggestive and devoid of dangers. In the present instance the writer has chosen the second of the two, and has made an intensive study of a single subject, namely himself.

THE SUBJECT

The subject's history in so far as it has any possible bearing on the present research is as follows: 1892-1895 intercollegiate athletics (Lacrosse); 1896-1905 in winter, excepting two months in mid-winter, vigorous exercise (one to two mile run several times a week); 1896-1907 in summer very strenuous mountain climbing sometimes involving feats of endurance. Since these dates systematic exercise has been

¹ A preliminary report of this work was made at the annual meeting of the American Physiological Society, December 1916 (5).

moderate and only for relatively short periods. Alcohol rarely and then in moderation, since 1907 not at all; no tobacco; coffee has been used occasionally. Between 1893 and 1911 acute dilatation occurred on four occasions. Recovery was always complete and prompt. Age 41 years in 1914 when these experiments were begun.

A partial physical examination of the subject made on April 27, 1916, gave the following data of possible relevancy to this research: Height 182.3 cm. weight 66.5 kilos (on June 7, 1916, 67.5 kilos); heart silhouette area 119.9 cm.² which is too small for age (43 years) and height, but normal for body weight according to Bardeen's tables. The estimated systolic out-put was 41 per cent (Bardeen). A brief discussion and skiagraph of this heart has already been published⁽¹⁾.

METHOD OF MAKING OBSERVATIONS

The *blood pressures* were determined by means of the auscultatory method. Whenever the routine determinations were taken during rest (tables A, B and C) from five to twelve (usually about seven) separate observations were made of both systolic and diastolic pressures. This precaution eliminated variations due to respiration and possible Mayer's waves.² If the first systolic readings were markedly higher than those which followed, these first readings (with corresponding diastolic readings) were rejected on the ground that their exceptionally high level was probably the result of previous exertion so that they were not comparable with the subsequent readings. In regard to this matter a considerable amount of care has always to be exercised since the systolic pressure may be influenced by activities which appear quite inconsiderable, as going up or down stairs, going from room to room, or even fetching and arranging the necessary apparatus. The satisfactory readings were averaged and it is these averages which are used in the compilation of the accompanying tables (tables A, B and C). All the calculations of the averages were performed twice³ independently to eliminate errors.

The counting of the *pulse rate* (one minute period) always followed immediately after the blood pressure determinations when the latter were made. When for any reason they were omitted, the pulse was counted until its rate became constant.

² The writer must again protest against the use of the term "Traube Herring wave" to designate vasomotor waves which are *not* synchronous with the respiratory movements (6), (7), (9).

³ I have much pleasure in thanking my daughter Emily for performing the tedious task of making one of the two series of calculations.

While making these observations the subject remained comfortably seated. In no case was there demonstrable any psychical variation of either pulse or pressure. As a matter of fact there were usually no emotions accompanying the observations except occasionally an intense impatience and desire to have done with the readings. This state of mind appeared not to affect the readings at all.

The observations of pulse and blood pressure fall naturally into two categories: the daily routine observations and the special observations made in connection with the special physical tests and exercises.

The routine observations may be divided into four sets according to the time of day at which they were taken. These times were *a*, immediately after rising (about 6 a.m.); *b*, just before lunch (12 noon); *c*, late afternoon (4:30 to 6 p.m.); *d*, before retiring (9:30 to 11:30, usually 10 p.m.). These four sets are referred to in this paper as "morning," "noon," "afternoon" and "evening" respectively. These routine examinations show the changes in the resting pressure and pulse rate which were induced by systematic exercise.

In addition to these there was, as stated above, another category of observations, namely those which were made in connection with specific exercises, during and after riding the cycle ergometer and those made after the three-mile runs. In both cases the observations were made before the exercises were part of the daily "routine" observations. These observations may be designated as "special" to distinguish them from the "routine" observations.

MODES OF EXERCISE

Series I. From December, 1913, to April 1, 1914, the subject took no exercise whatever. Soon after the latter date, however, he began to take exercise at first gently, later with some vigor. The routine observations are given in table A. The dates of occurrence of the exercise are seen in the accompanying calendar (1914). The exercise generally consisted in alternately walking and running for a distance of about three miles. As the strength of the subject improved he soon began to run the entire distance. It should be noted that owing to the age and prudence of the subject, the run was at a leisurely pace so that it required about thirty minutes for its accomplishment. There was no attempt made to shorten the time. The run ended in a short sprint which increased in vigor as the condition of the subject improved, but which did not appreciably shorten the time of the whole run. Both

before and after the period of systematic exercise (three-mile run) special tests were made by means of the bicycle ergometer. On these occasions the blood pressures and pulse rate were determined before, during⁴ and after the ride. The pulse rate during the test was obtained in part by palpation, in part from a record of the carotid pulse obtained by means of tambours with air transmission. No observations were made during the run, but only before and after. Those of the former period were in reality a part of the daily routine examinations already referred to. The method of securing the observations after exercise was the following:

On returning from the run the subject at once dropped into an arm-chair and in about one-half minute was beginning to make blood pressure determinations. These were made in rapid succession for several minutes. Meanwhile an assistant (the subject's wife, to whose assiduity the writer is much indebted) adjusted the cuff of the Erlanger apparatus to the subject's ankle and in this manner obtained a graphic record of the pulse rate. The desirability of making a graphic record of the pulse rate depends upon the fact that after exercise the rate of the pulse falls from its maximum too rapidly to be estimated by means of the watch and palpating finger. One must therefore measure the duration of single beats or of small groups of beats.

These facts are gathered together in the accompanying calendar (1914).

Calendar 1914

All exercise ceased early in December.

April 1. First ride on cycle ergometer. Special observations were made during and after ride.

April 2. Daily routine observations of pressure and pulse rate begun.

April 5 to April 20. Series of runs and walks in preparation for three mile runs. Special observations made only after runs.

April 22 to May 27. A series of three-mile runs, 14 in 35 days. Special observations made only after runs.

May 29 and June 8. Second and third rides on the cycle ergometer respectively. Special observations made during and after ride.

June 2. Daily routine observation discontinued.

Series II. In 1915 the observations were begun on March 5 and ended May 5. From early in December to March 13, the subject took no exercise whatever. He then began a systematic daily performance of

⁴ During the test the blood pressure observations were made by Professor Eyster, assisted by Miss Cantril. The latter embodied a presentation of a part of this work in her Master's thesis (2).

J. P. Müller's exercises in a moderated form (8). Later the exercises became more vigorous, but never reached in severity and tempo the standard set by Müller.

No special tests were made with the bicycle ergometer or in other ways, but routine observations were made of blood pressures and pulse rate from March 5 to April 19 (table B).

These facts are gathered together in the accompanying calendar (1915).

Calendar 1915

All exercise ceased early in December.

March 5. Daily routine observations of blood pressures and pulse rate begun.

March 13 to April 13. Modified Müller's exercises.

April 19. Daily routine observations discontinued.

Series III. In 1916 observations were begun on March 30 and continued until June 17 (table C). From December 1, 1915, to April 14, 1916, the subject had gone without exercise. On April 14 systematic exercises were begun. They consisted in riding upon the bicycle ergometer. On May 7 this exercise was discontinued. On June 6 and 7 two tests were made by means of the bicycle ergometer. Here, besides the daily routine observations of the pressures and pulse rate, the pressures (but not the pulse rate) were determined immediately after the rides upon the cycle ergometer in a manner similar to that described in the case of the three-mile runs undertaken in 1914. It should be noted in passing that the observations in 1916 were affected but not interrupted by two "colds," one at the beginning and one near the end of the period of observation. These facts are gathered together in the accompanying calendar (1916).

Calendar 1916

All exercise ceased early in December.

March 30. Daily routine observations begun.

April 3. First acute infection begins.

April 14 to May 7. Six rides on cycle ergometer followed by special determinations of blood pressures.

May 9 to June 3. Tennis.

June 6 and June 7. Two rides on cycle ergometer followed by special determination of blood pressures.

June 8. Second acute infection.

June 17. Daily routine observations discontinued.

ABBREVIATIONS

Since it is highly important that the reader should always have in mind just what is implied in the reference to, let us say, the series of observations performed in 1914, namely, that in this year the form of exercise taken consisted in a three-mile run, the writer has resorted to the following way of designating the three series of experiments, namely: '14-run, '15-gym, '16'-cy-ten, where the suffixes run, gym (gymnastics), cy (cycle ergometer) and ten (tennis) signify the variety or varieties of exercises peculiar to the series mentioned.

RESULTS I

Effect of training on the resting pulse rate. The effect of training upon the pulse of the subject while at "rest," that is to say, while doing only the ordinary work of the day and being therefore quite uninfluenced by any active physical exercise, was, with a single exception, to cause a decrease in the rate amounting to 3 to 9 beats per minute. (See table 1 and fig. 1.) The exception referred to is the rate on rising of series '15-gym where there is a slight increase in rate (one beat per minute). The rise is too small to lie beyond the limits of error but it is significant that in the morning observations of this series there was no decrease in rate. The exceptional nature of this result is probably due to the fact that in this series the exercise was exceptionally light (modified Müller's system).

TABLE 1
Effect of training on the resting pulse rate

SERIES	NUM- BER OF OBSER- VATIONS	TIME OF DAY	DATES (BEFORE)	AVER- AGE PULSE RATE		DATES (AFTER)
				Before	After	
'14-run..... {	9	Noon	April 2-25	54	51	May 10-June 2
	3	Afternoon	April 2-4	61	52	May 31-June 2
'16-cy-ten.... {	10	On rising	March 30-April 10*	58	52	May 29-June 7
	10	Noon	April 1-17†	58	50	May 29-June 7
'15-gym..... {	6	On rising	March 6-12	55	56	April 12-17**
	7	Noon	March 5-12	61	55	April 8-19

Table 1. The table shows that in the *first* column the series (date) and variety of exercise, given in order of the decreasing severity of the exercise; in the *second*, the number of observations from which the averages were obtained; in the *third*, the time of day at which the observations were made; *fourth*, the period (dates) during which observations were made prior to or early in the beginning of training; *fifth* and *sixth*, the average pulse rates corresponding to the dates given in columns four and seven respectively; *seventh*, the period (dates) during which the observations were made late in or subsequent to the period of training. * Omitting April 3 and 4 on account of sickness. ** Omitting April 13 when exercise immediately preceded the routine observations. † Omit-

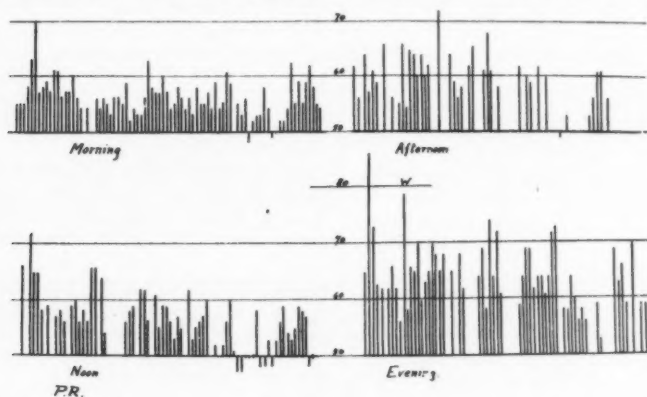


Fig. 1. Effect of training upon the resting pulse rate. The data presented in this figure are from series '16-cy-ten, table C. The lines in this figure represent pulse rates above or below 50 beats per minute. The lines are gathered into four groups corresponding to the time of day at which the observations were made. The observations in each group are arranged in order of time from left to right and wherever an observation is omitted a space has been left. Where the rate was just 50 per minute, a small stroke has been placed crossing the "50-line." Note the gradual decrease in the pulse rate with a slight increase at the end, the latter marking a corresponding decrease in the amount of physical exercise.

ting April 3, 4, and 5 on account of sickness. Evening observations which were influenced by previous periods of exercise, have not been used in making the averages. Note the decrease in the pulse rate after training.

Effect of training on the resting blood pressures. The effect of training on the resting blood pressures systolic and diastolic, is neither striking

nor constant at least not with exercises of the moderation employed in these experiments. Some changes have been noted of small amount and uncertain significance. For example, the behavior of the diastolic pressure in '14-run and '16-cy-ten is such that whether it falls or rises (the direction of the change depending upon the time of day at which the observations were made) there results an approach to 80 mm. (Table 2 and figs. 2 and 3). In this respect the noon observations of

TABLE 2
Effect of training on the resting blood pressures

SERIES	NUMBER OF OBSERVATIONS	TIME OF DAY	DATES (BEFORE)	AVERAGE BLOOD PRESSURES				DATES (AFTER)
				Before		After		
				S.	D.	D.	S.	
'14-run.....	6	Noon	April 2-13	121	90	116	88	May 23- June 30
	3	Afternoon	April 2-4	123	97	120	90	May 27-29
'16-cy-ten.....	10	On rising	April 6-15	102	76	106	77	June 8-17
	10	Noon	April 6-18	115	85	115	82	June 8-17
	5	Afternoon	April 5-10	115	84	117	82	June 6-11
	7	Evening	April 4-17	112	78	116	78	June 8-17
'15-gym.....	6	On rising	March 6-12	111	85	110	80	April 12-17
	10	Noon	March 5-15	112	84	120	91	April 8-19

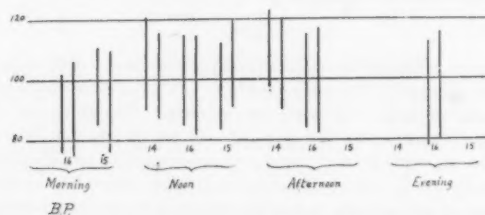


Fig. 2. Effect of training on the resting blood pressures. The numerals at the extreme left represent mm. Hg. The vertical lines are the pulse pressures, the upper end of each being at the systolic level, the lower at the diastolic level. The numerals placed below designate by dates the series of experiments to which the two lines immediately above each belong. Of each pair of vertical lines the one to the left represents the pressure before training; that to the right, the pressures after training. The series (date numerals) are arranged in order of decreasing severity of the exercise. Note the absence of any conspicuous or constant effect of training upon the systolic and diastolic pressures, at least when the exercise is of the moderation represented by these experiments. Possibly the diastolic pressure tends to approach 80 mm.

'15-gym differ from the other two series but whether this was due to the difference in kind or in severity of the exercise or to some other cause, is purely conjectural. It is also to be noted that the change in the relation of the systolic to the diastolic pressure in all three series was usually such as to increase the pulse pressure (*vide infra*).

Table 2. The table shows in the *first* column the series (date) and the variety of exercise, given in the order of the decreasing severity of the exercise; in the *second*, the number of observations from which the averages were obtained; *third*, the time of day at which the observations were made; *fourth*, the period (dates) during which observations were made prior to or early in the beginning of the training; *fifth and sixth*, the average systolic and diastolic pressures corresponding to the dates in columns four and seven respectively; *seventh*, the period (dates) during which observations were made late in or subsequent to the period

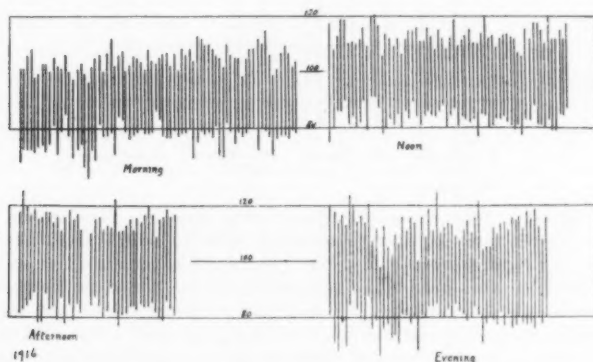


Fig. 3. Development of the effect of training upon the blood pressures. In as much as the observations are more complete for '16-cy-ten than for either of the other series, it has seemed justifiable to devote to their presentation a separate figure. This figure is based upon the entire number of observations comprised in the series in question (table C). In this figure the vertical lines are the pulse pressure, the upper end of each being at the systolic level, the lower end at the diastolic level. The horizontal lines of reference represent 120 mm. Hg. (upper line) and 80 mm. Hg. (lower line) respectively. The vertical lines are divided into four groups corresponding to the observations made at different times of the day. The changes in the pressures are appreciated best when the observer looks at the chart from the side and foreshortens it by holding it at an obtuse angle to the line of vision. Note the gradual developments of the changes in the blood pressures, of which figure 2 gives only the final outcome. One may also obtain from this chart some idea of the character of the diurnal variations in the blood pressures, to which special reference will be made later.

of training. The evening observations which were influenced by previous periods of exercise, have not been used in making the averages.

Effect of training on the resting pulse pressures. The effect of training upon the pulse pressure during rest is almost always in the direction of an increase. Sometimes this increase is small (3 mm.), at others larger (6 mm.), but in only one instance was there a decrease (3 mm.) namely in '14-run, noon. (Table 3 and also fig. 4.) The writer has been unable to assign a plausible reason for the exception mentioned above. Numerically it was due, at least in part, to a period of high systolic pressure during which the series '14-run was begun to a period of high diastolic pressure during the last few days of the series.

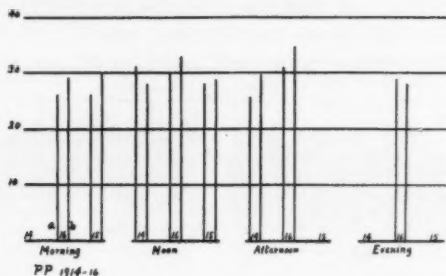


Fig. 4. Effect of training on the resting pulse pressure. The values used in this figure are the same as those presented in table 3. The numerals at the extreme left and right represent mm. Hg. The vertical lines are the pulse pressures. The numerals placed below indicate the series (dates) to which the two lines immediately above belong. Of each pair of vertical lines, the one to the left represents the pulse pressures before training and that to the right the pulse pressures after training. The date numerals are arranged in order of the severity of the exercise from left to right. Note that in almost every case there is an increase in the pulse pressure as the result of training, but that the increase is often quite small.

Effect of training on the product $P. R. \times P. P.$ during rest. The product of the pulse rate times the pulse pressure is of interest since it is possibly (3), (4) an index of "minute volume" (output of the heart per minute). It has been seen above that as a result of training the pulse rate falls while the pulse pressure rises in value. The product would consequently tend to remain unchanged and would be entirely unchanged if the variations in rate and pulse pressure were proportional as well as being in the opposite direction. This is, however, not the case. The product may be found to have risen or fallen so that the compensation (if we may speak of such) is not exact but sometimes falls short and sometimes

TABLE 3

Effect of training on the pulse pressure and on the product P. P. \times P. P. during rest

SERIES	TIME OF DAY	PULSE RATE \times PULSE PRESSURE			
		Before		After	
		P. R.	P. P.	P. R.	P. P.
'14-run.....	Noon	55	$\times 31 = 1705$	1512	$= 54 \times 28$
	Afternoon	61	$\times 26 = 1580$	1740	$= 58 \times 30$
'16-cy-ten.....	On rising	58	$\times 26 = 1508$	1653	$= 57 \times 29$
	Noon	58	$\times 30 = 1740$	1815	$= 55 \times 33$
	Afternoon	60	$\times 31 = 1860$	1991	$= 57 \times 35$
	Evening	62*	$\times 34 = 2108$	2356	$= 62 \times 38$
'15-gym.....	On rising	55	$\times 26 = 1400$	1680	$= 56 \times 30$
	Noon	60	$\times 28 = 1680$	1595	$= 55 \times 29$

is excessive. An increase in the product was of more frequent occurrence than a decrease. These differences are very slight and the preponderance of the increase over the decrease may not be significant. (Table 3, and fig. 5.)

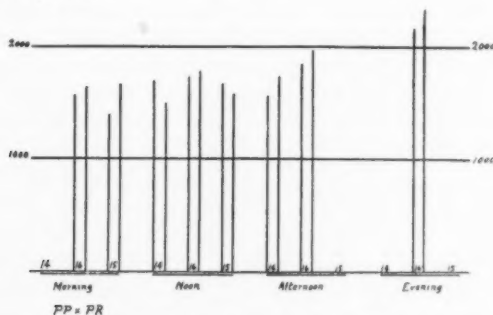


Fig. 5. Effect of training on the product of the pulse rate and pulse pressure P. R. \times P. P. during rest. This product is of interest from the fact that it may represent the cardiac output per minute (minute volume). The data from which this figure was constructed are those presented in table 3. The numerals at the extreme left and right represent mm. Hg. The vertical lines represent the product P. R. \times P. P. The numerals placed below indicate the series (dates) of experiments to which the two lines immediately above belong. Of each pair of vertical lines the one to the left represents the product before training and that to the right the product after training. The series (date numerals) are arranged in order of the decreasing severity of the exercise from left to right. Note that in almost every case there is an increase in the product as the result of training although this increase is often quite small.

There is in the product under consideration a diurnal variation of the nature of an increase throughout the day. This variation is apparently not affected by training.

Table 3. The table shows in the *first* column the series (date) and the variety of exercise, given in the order of the severity of the exercise; *second*, the time of day at which the observations were made; *third*, the pulse rates corresponding to the pulse pressures in the next column; *fourth*, the pulse pressure before or early in the period of training, derived in great measure from the data given in table 2; *fifth*, the product of columns three and four; *sixth*, the product of columns seven and eight, placed next to column five for convenience of comparison; *seventh*, pulse rates corresponding to pulse pressure in the last column; *eighth*, the pulse pressure after or late in the period of training, derived in great measure from the data given in table 2. *From April 2-11. *Note that the pulse pressure and the values of $P. R. \times P. P.$ are usually greater "after" than "before."*

Table 4. The data are from '16-cy-ten. This table shows in the *first* column the dates upon which the observations were made. On these dates there was no afternoon exercise or other unusual event to influence the evening values; the *second* to *fifth* columns are pulse rates and require no explanation. The figures are divided into two sets (April 6 to May 2 and May 6 to 31). The first set occurs in the earlier part of the period of training, the second set in the latter part. Below these columns are placed the averages. *Note that the pulse rate shows no striking change which might be attributed to training in the character of the diurnal variations but that the extent of the variations is slightly increased.*

Effect of training on the diurnal variations of the resting pulse rate. The effect of training upon the resting pulse rate is not of the same magnitude for all times of the day (table 4). The most pronounced slowing is that of the pulse rates for noon and late afternoon, namely, five and four beats respectively as compared with three beats per minute in the morning and two in the evening. An unequally distributed change of this kind would naturally alter the *form* of the diurnal pulse curve. This alteration is, however, so small that it may lie entirely within the limits of error.

The curve is altered also in its *extent*, for if the comparison be made between the amount of the average daily variation before and after training, the greater variation is found to occur after training. The increase in variation is, however, very small, amounting to only 1.3 beats and may well lie within the limits of error or if real be too small to be significant.

TABLE 4

Effect of training on the diurnal variations of the pulse rate during rest

DATE	MORNING	NOON	AFTERNOON	EVENING
April 6.....	58	58	61	62
April 11.....	56	58	56	56
April 17.....	50	58	64	60
April 19.....	54	66	64	65
April 20.....	56	66	60	70
April 28.....	54	56	59	62
May 2.....	63	62	62	64
Average (before).....	58	61	63	63
May 6.....	60	61	61	64
May 8.....	54	59	61	61
May 17.....	55	55	62	62
May 19.....	54	57	60	64
May 20.....	59	60	59	61
May 29.....	48	47	49	56
May 31.....	53	50	53	56
Average (after).....	55	56	57	61

Effect of training on the diurnal variations of the blood pressures during rest. The diurnal variations of blood pressures in one series of observations ('16-cy-ten) are also shown in figure 3. From this series there have been selected all the complete diurnal cycles which have not been interfered with in respect to the evening observations by a period of exercise preceding the latter or by any other disturbing influence. When this was done the number of such cycles was found to be fourteen.

The variations may be regarded from two points of view. First, one may consider the separate daily curves to note any variation in the form of these curves; and second, one may compare all the absolute values of the pressures at different periods of the day. (For example, we may compare all the noon pressures).

If we examine the daily curves (fig. 6) it is found that the systolic pressures show seven different rhythms (table 5) of which two predominate, namely, *a*, a rise to a maximum at noon followed by a fall in the afternoon and evening; and *b*, the noon maximum is sustained until afternoon and the fall is not observed until evening.

Table 5. The data from which this table is derived are those which have formed the basis of figure 6. They represent observations made on fourteen days of the series '16-cy-ten. The table shows in the *first* column the number of instances in which the rhythm, which immediately follows, has occurred; in the *second*, the character of the change which took place between the morning and the noon observations; the *third* column, between the noon and the afternoon observations; the *fourth*, between the afternoon and the evening observations. *Note that the usual systolic rhythms are "up-no change-up" and "up-up-down," while the usual diastolic rhythms are "up-down-down" and "up-up-down."*

On the other hand the changes in the diastolic pressure are more constant. Here only three rhythms occur (table 5) one of which appears but once. The remaining two are, *a*, a rise to noon and then a fall; *b*, a rise to afternoon and then a fall.

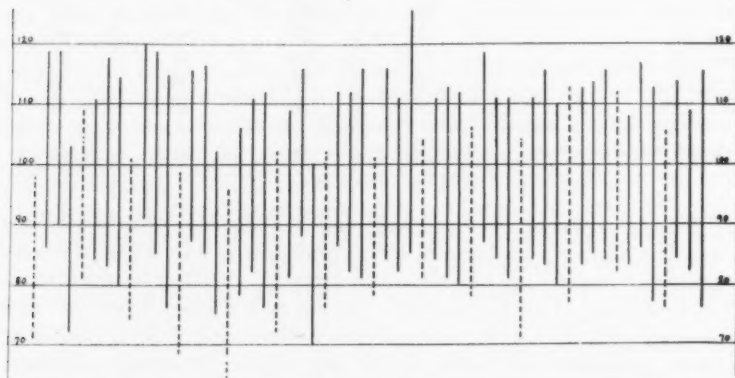


Fig. 6. The daily variations in systolic, diastolic and pulse pressure during training. The observations from which this figure has been constructed were made on fourteen days of the series '16-cy-ten. The numerals at the extreme left and right represent mm. Hg. Vertical bars are pulse pressures, upper end of each being at systolic level, lower at the diastolic. Dotted bars represent morning pressures. *Note increase in diurnal variations of systolic pressure, decrease in diurnal variations of diastolic pressure, and that the character of the daily rhythms is unchanged.*

The pulse pressure corresponding to the systolic and diastolic pressures just mentioned show daily rhythms which are remarkably variable. In these fourteen days there are twelve different rhythms of which two are repeated (making the total of fourteen cycles).

There seems to be no evidence in these qualitative data that training produces any effect upon the inter-relations of the four points on the

diurnal curves of systolic, diastolic or pulse pressure. In other words, we do not find that one form of diurnal curve predominates before training while another predominates afterwards.

The effect of training upon the absolute values of the blood pressures observed at different times of the day has already been referred to. By way of recapitulation it may be said that (omitting '15-gym) the morning pressures are raised, the noon lowered while the afternoon and evening pulse pressures are increased. Moreover there is a gradual reduction of the amount of diurnal variation of the blood pressures (as shown in fig. 6).

The amount of this reduction of the diurnal variations may be expressed as follows. If we observe the values of the systolic pressure

TABLE 5
Diurnal rhythms in systolic and diastolic pressure

	NUMBER OF INSTANCES	MORNING TO NOON	NOON TO AFTERNOON	AFTERNOON TO EVENING
Systolic pressure.....	4	Rise	No change	Fall
	4	Rise	Rise	Fall
	1	Rise	Fall	Rise
	1	Rise	Fall	No change
	1	Rise	Rise	Rise
	1	Rise	No change	Rise
	1	Fall	Rise	Fall
	8	Rise	Fall	Fall
Diastolic pressure.....	5	Rise	Rise	Fall
	1	Rise	Fall	Rise

for one day, and subtract the minimum systolic pressure from the maximum systolic pressure we get a figure indicative of the difference between the extremes of systolic variation on this day. If the values obtained for several days selected from the period preceding or early in training be compared with the values similarly selected from a period later in or subsequent to the training, then the latter are found to be less than the former by 20 per cent. If the values of the diastolic pressure be treated in the same manner, the variations after training are found to have decreased by 50 per cent. Finally if the difference between the maximum and minimum pulse pressure be considered, one finds a decrease of 10 per cent only, which the writer does not think is large enough to be safely beyond the limits of error. Consequently, although there is as has been shown an increase in the pulse pressure

after training, yet the diurnal fluctuations in the size of the pulse pressure have not been positively shown to vary. The product of P.R. \times P.P. shows a diurnal variation of the nature of an increase throughout the day. The character of this variation seems not to be affected by training.

RESULTS II

Effect of training and practice on the reaction to exercise of blood pressures and pulse rate. The reaction to exercise depends upon two factors. If a subject be tested on a bicycle ergometer and then runs several miles every few days for several weeks, and if he be finally tested again with the ergometer, the change in his reaction is due to an improvement in his general physical condition which is the result of this systematic exercise. This state or condition we have called "training." If on the other hand the reaction of the subject to the first run be compared with the reaction of the subject to the last run, then the change is attributable to two factors: first, to what has been called above "training," and second, to "practice." The latter is in all probability a condition of neuromuscular adaptation to a certain special sort of exercise, in the case cited, running. The reaction to exercise is modified by these two factors. If the subject is in training or has practiced he reacts in one way; if not, he reacts differently. It is these differences which constitute the topic of the present section.

That practice and training are quite different states of efficiency is shown by such observations as the following: A young woman who was an expert swimmer and possessed great physical strength, was seized with an acute dilatation of the heart on her first attempt at mountain climbing, the tax not being a severe one. By beginning again with great caution after a few days of rest, and progressively increasing the severity of the climbing, she became at the end of a few weeks as efficient in this form of exertion as in those to which she had already been inured, namely, rowing and swimming. Here the subject though trained was not practiced. And the result when practice had been added to training was quite different from the effect when the condition was one of training only. It is not possible to separate with entire satisfaction the effects of practice from those of training and practice combined, but it is readily possible to separate the effect of training from this combination as has been intimated.

It is exceedingly important to remember that throughout the present study of the reaction to exercise before and after training, *the amount of*

exercise is not a constant factor. In the beginning of the experiments it was thought desirable to keep the amount of work done as nearly constant as possible. That would have made the results obtained show the effect of practice and training on the circulatory reaction to a fixed amount of work. But in the enthusiasm and delight of physical activity, it was found unbearably irksome to restrain the trained body. In every cycle ride the subject when once underway proceeded forthwith to pedal joyously. In the case of the three-mile run the natural beauty of the environment proved a sufficient distraction to permit an almost uniform rate of progression, but the approaching of home called forth an inevitable sprint which increased in vigor with training and practice. What these experiments show is the effect of training and practice upon the reaction of the pulse rate and blood pressures of a subject who (within the limits imposed by prudence) performs as vigorously as possible on every cycle ride and three-mile finish.

With the recently improved facilities of this laboratory it is practically certain that studies will soon be made of the reaction to a standardized task, but it cannot be too frequently reiterated that the present article is *not* such a study.

It was found that the same qualitative results were obtained whether the observations were made during the latter part of the period of exercise or immediately after exercise. But quantitatively the changes noted after exercise were, as might be expected, just a little less in extent and the condition continued to approach normal with the lapse of time.

In some of the instances described in this section the observations were made before, during and after the test exercises (cycle ergometer), while in others they were made only before and after exercise (cycle ergometer and three-mile run).

The reaction of the blood pressures and pulse rate to exercise is well known. It consists in a rise in the systolic and pulse pressures and to a much less extent of the diastolic pressure. The pulse rate is also markedly increased.

Effect of training only. The effect produced by training on the circulatory reaction (fig. 7) is as follows: *a*, the systolic pressure rises more rapidly and much higher than is the case in the untrained individual; *b*, the diastolic pressure often returns to normal before the cessation of the exercise; *c*, the pulse pressure is enormously increased. Before training the rise in pulse pressure was from 38 (normal) to 62, after training from 37 to 114. *d*, The product $P.R. \times P.P.$ is also greatly increased (before training the rise was from 2660 (normal) to 6820, after

training from 2220 to 12540). *e*, The change in the pulse rate is but little affected; *f*, moreover with less effort more mechanical work is done.

Effect of practice only. No systematic attempt was made to dissociate training from practice so that a separate study of the latter might be made. There was, however, an incidental observation which is worth recording. In the series '16-cy-ten, it was found that the blood pressure reaction after the second ride was remarkably different from that following the first ride. This change in the reaction was of the nature of an increase in the systolic pressure and pulse pressure and subjectively of a decrease in the discomfort.

It seems more improbable that a single ride should have put the subject into a condition of training than that he should have experienced

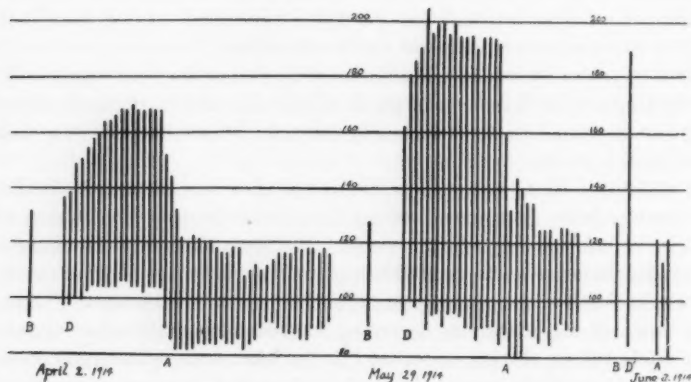


Fig. 7. Effect of training on the reaction of the pulse rate and blood pressures to cycle riding. The numerals in vertical columns represent mm. Hg. The vertical lines are the pulse pressures, the upper end of each being at the systolic level, the lower at the diastolic level. The letters *B*, *D* and *A* stand for "before," "during" and "after" respectively. April 1: immediately after *B*, the cycle ride began and observations were made at frequent intervals both during the ride, *D* and afterward, *A*. Here $\text{kilos} \times \text{revolutions} = 7 \times 3276 = 23,849$ and $\text{P. R.} \times \text{P. P.} = 110 \times 60 = 6820$, during exercise. May 29: as before, but *S* is fifty-five minutes later than the end of *A*. Here $\text{kilos} \times \text{revolutions} = 7 \times 4423 = 30,961$ and $\text{P. R.} \times \text{P. P.} = 110 \times 114 = 12,540$. June 8: *B* is as before but of the pressures recorded during exercise a single pair (that giving the maximum pulse pressure) is here drawn, *D*, and only the last three pairs of observations from the period after exercise are given, *A*. Note that after training there is an increase in the reaction to exercise in respect to the systolic and pulse pressures but a decrease in the diastolic pressure.

the beneficial effects of a little practice. But however this may be, the fact remains that a single ride produced a pronounced effect. (Table 6 and fig. 8).

TABLE 6

Effect of practice and of training and practice on the reaction of the blood pressures to exercise (cycle riding)

DATE	KILOS	REVOLU- TION	K. X R.	MINUTES	BEFORE EXERCISE					AFTER EXERCISE				
					S.	D.	P.P.	P.R.	P.R. X P.P.	S.	D.	P.P.	P.R. X P.P.	P.P.
April 14.....	6	3900	23,400	25	114	78	36	66	2376	120	74	46	(5060)	
													(5520)	
													(5980)	
April 16.....	6	5399	32,394	30	116	77	39	65	2535	140	80	60	(6600)	
													(7200)	
													(7800)	
April 29.....	8	6113	48,904	30	111	84	27	56	1512	146	76	70	(7700)	
													(8400)	
													(9100)	
May 3.....	8	5790	46,320	30	112	90	32	66	2112	140	76	64	(7040)	
													(7680)	
													(8320)	

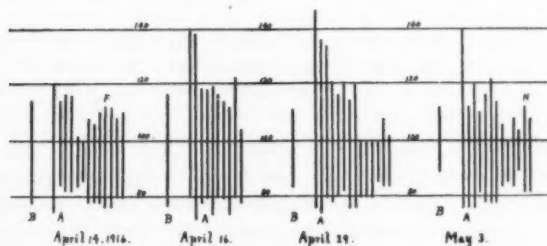


Fig. 8. Effect of practice and training on the reaction of the blood pressures to cycle riding. The data corresponding to this figure are shown in table 6. They are from the series '16-cy-ten. The numerals placed in the vertical columns represent mm. Hg. The vertical lines are the pulse pressures, the upper end of each being at the systolic level, the lower at the diastolic level. The figure shows observations taken before B and immediately after A, riding the bicycle ergometer. At F, there was a transitory feeling of faintness; at N, an equally transitory feeling of nausea. The duration of the rides were in three cases thirty minutes, in one case (April 14) twenty-five minutes. Kilos \times revolutions = (April 14) 23,400; (April 16) = 32,394; (April 29) = 48,904; (May 3) = 46,320. Note that after training the heart is capable of a much greater reaction without untoward symptoms.

Table 6. The data are from the series '16-cy-ten and the table corresponds to figure 8. In the *first* column are given the dates of the experiments; in the *second*, the weight of the brake, in kilos; *third*, the number of revolutions of the cycle ergometer; *fourth*, the product of the weight times the revolutions; *fifth*, the duration of the ride; *sixth* to *tenth* inclusive, blood pressures, pulse rate and their derivatives, taken before exercise; *eleventh* to *fourteenth* inclusive, the blood pressures, pulse rate and their derivatives observed after exercise with the exception to be mentioned immediately, namely, that as the P.R. was not observed, the numerals in parentheses were calculated after assuming a rate of 110, 120 or 130 beats per minute, and are presented as suggestive merely. *Note that the practice and training exaggerate the increase in systolic pressure and pulse pressure and assuming that the difference in increase of the pulse rate was not more than twenty beats (cf. table 9) that the product $P.R. \times P.P.$ is also increased.*

TABLE 7

Effect of training and practice on the reaction of the blood pressures and pulse rate to exercise (three-mile run)

DATE	BEFORE EXERCISE					AFTER EXERCISE				
	S.	D.	P.P.	P.R.	$P.R. \times P.P.$	S.	D.	P.P.	P.R.	$P.R. \times P.P.$
April 17.....	128	90	38	58	2204	138	90	48	100	4800
May 8.....	111	78	33	55	2815	164	80	84	96	8064
May 14.....	110	83	27	65	1701	168	76	92	108	9936

Combined effect of training and practice. These effects were studied in two series of experiments. In the *first* ('14-run) observations were made of both pulse rate and blood pressures while in the second ('16-cy) the blood pressure only was determined. In both, the observations were made before and again immediately after exercise. In respect to the blood pressures, the results were essentially the same in both series and were in accord with those obtained by training alone. In the first series ('14-run) *a*, there was an increase in the rise of the systolic pressure; *b*, the change in diastolic pressure was not markedly affected; *c*, the pulse pressure was enormously increased; *d*, the product $P.R. \times P.P.$ was also greatly increased. Also the mechanical work done was greater with apparently less exertion. *e*, The pulse rate was decreased (cf. table 9). Unfortunately the negative phases cannot be compared in this series because the late observations were not made at the same interval of time after the cycle rides. (Table 7, fig. 9).

Table 7. The data are from the series '14-run and the table corresponds to figure 9. The table requires no further explanation. *Note that the training and practice exaggerate the increase in systolic pressure, pulse pressure and the product $P.R. \times P.P.$ while the change in the pulse rate is unaffected.*

In the *second* series ('16-cy-ten) the first exercise of the season was a cycle ride taking place on April 14. (Table 8, fig. 10). On April 29 the ninth cycle ride took place. On June 6 and 7 came the tenth and eleventh rides respectively. Between the first and ninth rides cycle

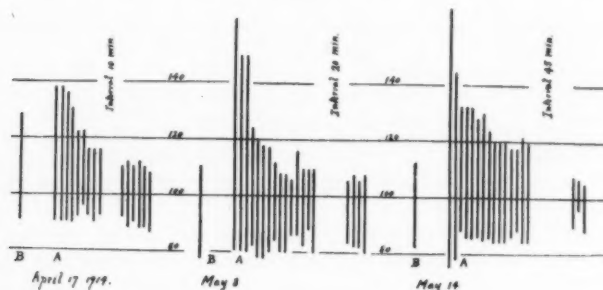


Fig. 9. Effect of training and practice on the reaction of the blood pressure to the three-mile run. The numerical data corresponding to this figure are shown in table 7. They are from series '14-run. The numerals in vertical columns represent mm. Hg. The vertical lines are the pulse pressures, the upper end of each being at the systolic level while the lower end is at the diastolic level. *B* indicates observations made immediately before and *A*, immediately after exercise. Here $P. R. \times P. P.$ (April 17) = 4800; (May 8) = 8064; (May 14) = 9936. The observations made after the exercise are in each case interrupted for a few minutes as indicated in the figure. *Note that after training there is an increase in the reaction to exercise in respect to the systolic and pulse pressures.*

riding was the only form of exercise. Between the ninth and tenth rides there intervened several weeks of tennis playing. Consequently in the first period the cycle ergometer tested the effect of both training and practice while in the second period it tested only that of training. The second period, however, was not particularly significant because the subject had just passed through a course of exercise which had already removed most of the effects of the prolonged inactivity which had preceded the series. On comparing the effect of the first cycle ride with that of the ninth, one finds the same results as in the first series with respect to the blood pressure. Moreover in comparing the effect

of the ninth ride with that of the tenth and eleventh, one finds that the changes in the reaction to exercise are no greater after nine rides and several weeks of tennis than after nine rides alone. In the former case the negative phase is not quite so conspicuous as in the latter which suggests that the result of the further training may have been to permit an increase of this phase. This conclusion is nevertheless insecurely based since the negative phase, properly so called, would not be expected to occur until some time subsequent to the last observations made in each of the riding tests in question.

TABLE 8

Effect of practice and training on the reaction of the blood pressure to exercise (cycle riding)

DATE	KILOS	REVOLU- TION	K. X R.	MINUTES	BEFORE EXERCISE					AFTER EXERCISE			
					S.	D.	P.P.	P.R.	P.R. X P.P.	S.	D.	P.P.	P.R. X P.P.
April 14.....	6	3900	23,400	25	114	78	36	66	2376	120	74	46	(5060) (5520) (5980)
April 29.....	8	6113	48,904	30	111	84	27	56	1215	146	76	70	(7700) (8400) (9100)
June 2.....	—	—	—	—	117	80	37	53	1961	144	70	74	(8140) (8880) (9620)
June 7.....	8	7007	56,056	30	115	78	37	56	2072	144	80	64	(7040) (7680) (8320)

Table 8. The data from '16-cy-ten and the table corresponds to figure 10. In the *first* column are given the dates of the experiments; in the *second*, the weight of the break; *third*, the number of revolutions of the cycle-ergometer; *fourth*, the product of the weight times the revolutions; *fifth*, the duration of the ride; *sixth* to *tenth* inclusive, blood pressures, pulse rate and their derivatives, taken before the exercise; *eleventh* to *sixteenth* inclusive, the blood pressures, pulse rate and their derivatives observed after the exercise, the exception to be mentioned immediately, namely, since the P.R. was not observed, the numerals in parentheses were calculated on the assumption of a rate of 110, 120 or 130 beats per minute, and are presented as suggestive merely. *Note that the practice and training exaggerate the increase in systolic pressure and pulse pressure, and assuming that the increase of the pulse rate is in-*

creased not more than twenty beats (see table 9) that the product $P.R. \times P.P.$ is also increased.

From the *subjective side* the effect of training alone and of training and practice combined is to enable the heart to work more vigorously without untoward symptoms. Although before training or practice the pulse pressure (systolic output?) is relatively small during (and just after) exercise, the distress is considerable; later, after training or practice, although the pulse pressure is very much greater, the individual suffers no subjective embarrassment whatever.

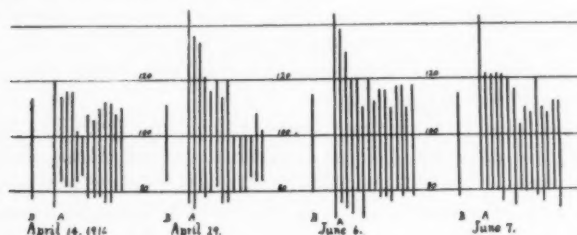


Fig. 10. Effect of practice and of training and practice (?) on the reaction of the blood pressure to cycle riding. The data corresponding to this figure are shown in table 8. They are from series '16-cy-ten. The numerals placed in the vertical columns represent mm. Hg. The vertical lines are the pulse pressures, the upper end of each being at the systolic level, the lower at the diastolic level. The observations were made before, B, and immediately after, A, riding the bicycle ergometer. Here kilos \times revolutions (April 14) = 23,400; (April 29) = 48,904; (June 7) = 56,056. The duration of the exercise was twenty-five minutes in one case (April 14), thirty minutes in the other two. Note that after training there is an increase in the reaction to exercise in respect to the systolic and pulse pressures.

Effect of training and practice on the pulse rate after exercise and on its return to normal. A few observations have been made with reference to the effect of practice and training *a*, upon the increase of the pulse rate due to exercise, and *b*, upon the rapidity of the return of the pulse rate to normal after exercise has ceased.

a. If the relevant data from series '14-run be divided into two parts, the first of which represents the results obtained early in the period of training and practice, and the second the data obtained later in this period, it is possible to make certain comparisons (table 9). If one compares the maximum rate after exercise during the first half period with the corresponding rate during the second half period, one finds that the former exceeds the latter (150 beats per minute as compared with 126). Again if one compares the average rate during the first half

period with the average rate during the second half period, one finds that once more the former exceeds the latter (119 and 127 respectively). It is quite probable that these differences would have been greater but for certain counteracting influences, namely *a*, that the final sprint was more vigorous as the condition of the runner improved, and *b*, that the pulse record was probably begun a trifle earlier (that is, with less loss of time) as the assistant became more deft in adjusting and inflating the cuff upon the ankle. It is possible that the fact that during the last two days (May 26 and 27) the weather was unusually hot may also have tended to raise the pulse. The resting pulse of this subject is faster in warm weather than in cool, and it may be that the pulse in reacting to exercise rises higher during warm than during cold weather, but this has not been ascertained.

Table 9. The data are from series '14-run and represent the pulse after a three-mile run. During the two hours referred to in column eight, the subject bathed and dined. The values given (pulse rates per minute) were calculated from the rates for 5 to 10 seconds, consequently all errors are highly magnified. This is why columns two and three, and four and five have been averaged together (average II). The values used in making the averages are enclosed in parenthesis. The value 132* is so high that it arouses distrust as to its accuracy, it is therefore omitted from one average and included in the other (*). *Note that the averages are lower "immediately after" running in the trained and practiced subject, but that at the end of two minutes this difference has considerably decreased.*

b. After exercise the pulse rate falls at first rapidly and then more slowly. Even at the end of five hours it was still above normal as can be seen from the following values, namely, 65.5 (62 if we omit the warm days May 26 and 27). In series '14-run, the pulse rate at the time of the retiring was 65.5 (62 if we omit May 26 and 27, when the weather was unusually warm) on days on which the subject exercised, while on the resting days, the corresponding figure was only 56. This tardiness in the return of the pulse to normal is seen again in series '16-cy-ten. Here the average pulse rate on retiring was 68 on days of cycle riding and on days of resting 62. (Table C).

For comparing the readiness with which the pulse rate returned to normal during the first part of the period of training with the corresponding values for the second part, one turns again to series '14-run. Here observations made *two minutes after cessation* of exercise were divided into two sets corresponding to the first part of the period of

training, and to the second part respectively. Such a comparison (table 9) shows that the difference between the averages of the rates during these two half-periods has decreased below what it was immediately after exercise. In other words, the higher pulse rate has fallen more rapidly than the lower although neither had of course as yet reached the normal level.

TABLE 9

Effect of training and practice upon the return of the pulse rates to normal after exercise

DATE	IMMEDIATELY AFTER RUN	10 SECONDS	1 MINUTE	2 MINUTES	3 MINUTES	5 MINUTES	ABOUT 2 HOURS	ABOUT 5 HOURS
April 17.....	100				80			
April 18.....	(102)	(96)	(90)	(80)				
April 27.....	(150)	(150)	(114)	(92)	88			
April 30.....	(132)	(132)	(108)	(94)				
May 1.....	(150)	(114)	(132)*	(92)				
May 2.....	(120)	(102)	(108)	(96)			71	56
May 6.....	(120)	(108)	(108)	(90)	90			58
May 7.....		108		90	96	82	72	63
May 8.....	96	102		90	96	86		64
May 13.....	(126)	(102)	(114)	(90)	90	88	70	63
May 14.....	(108)	(108)	(102)	(96)	96	92	78	64
May 22.....	(120)	(108)	(102)	(96)	76	90	77	70
May 23.....	(108)	(114)	(102)	(96)	90	88	78	66
May 26.....	(126)	(114)	(120)	(114)	102	108	80	73
May 27.....	126	120	120		102	98	76	71
Average I.....	129	117	126* 105	90	} April 18-May 6 inclusive			
Average II.....		123		108* 97				
Average I.....	117	109	108	92	} May 13-26 inclusive			
Average II.....		113		100				

Turning the attention to the *evening pulse rate*, that is the rate at about five hours after the cessation of the exercise, one finds noteworthy data in series '16-cy-ten. If this series be divided into two parts and comparison be made between the average evening pulse rate during the first part (April 14 to May 15 inclusive) with the average evening pulse rate during the second part (May 16 to June 3 inclusive) selecting in both cases the days upon which exercise was performed, the former is

found to be 68.7, the latter 61.4. From this one would conclude either that the effect of training and practice favored the return of the pulse rate to normal, or that the difference of rate of return to normal resulted from the difference in the form of exercise, namely, cycle riding in the first case and tennis in the second.⁵ To the writer, the latter alternative seems to be the less important factor.⁶

RESULTS III

Effect of training on infection. The effect of training on the course of an acute naso-pharyngeal infection was noted during the period of observation in 1916. The subject was attacked with the malady in question on April 3 and again on June 8. Both attacks began with nasal and pharyngeal inflammation and marked constitutional symptoms. Then, after a period of rapid convalescence, a laryngitis set in with a return of the constitutional symptoms. This in turn gave place to complete recovery.

On perusal of the blood pressure readings (see table C and fig. 3) the writer cannot see that the blood pressure has been affected at all by either infection, even after the data were charted with reference to the diurnal changes and subjected to close scrutiny no effect could be detected. The pulse rate however shows a great increase during the first attack, but a relatively small one during the second (see fig. 11).

It should be noted that the symptoms in both cases (both local and constitutional) occurred before the change in pulse rate.

The interest in these attacks lies in the facts, *a*, that the observations of blood pressure and pulse rate were begun a considerable time before the infection occurred and were continued for some time after and the abnormal phenomena are therefore carefully controlled; and *b*, that the infections in question were very similar to each other and also to other infections not infrequently experienced by the subject, which run in every case a perfectly definite and predicable course, independent to a

⁵ Unfortunately, in the first part of series '14-run observations were rarely made after the end of two minutes, so that a conclusive comparison cannot be made between the evening pulses of the first and second series. This is the more to be regretted since the few values obtained seemed to contradict the conclusions drawn from series '16-cy-ten.

⁶ Indeed since it is often found that prolonged exercise favors a retarded return of the pulse to normal, one might expect that, after one and a half to two hours of tennis, the pulse would return to normal more slowly than after the thirty-minute cycle rides.

great degree of such differences in the weather conditions as distinguish early April from early June in Madison in 1916. It seems probable therefore that the only variable factor and hence the cause of any difference between these two attacks is the fact that the subject was in bad physical condition during the first attack while the contrary was the case during the second attack.

Effect of acute infection on the response of the pulse rate to exercise. It is of interest and also is germane to the present topic to note at this point the effect of an acute infection upon the response of the pulse rate to exercise in a case of acute naso-pharyngeal affection. The writer has long been familiar with the feeling that the heart beats more rapidly

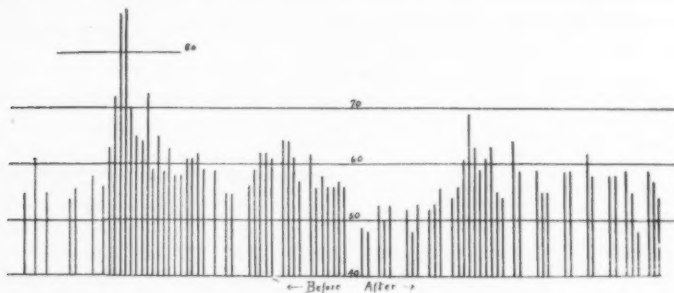


Fig. 11. Effect of training upon the pulse rate during an acute infection. The figures in the ventricular column signify pulse beats per minute. The ventricular lines show the pulse rate in series '16-cy-ten'. They are arranged in the order of time. Wherever the observer failed to determine the pulse rate at the appointed hour, a blank space has been left. The observations fall into two groups (1) early in the series (2) late in the series; in other words 'before' and 'after' training. The maximum pulse rate 'before' occurs on the evening of the first day (April 3) upon which symptoms of the first infection were observed; that 'after' on the evening of the first day (June 8) of the symptoms of the second infection. Note that the maximum before training is much higher than that after training.

on running up stairs when one has a "cold" than under normal circumstances. No careful observations were made until May, 1919. At that time the writer was engaged in a series of experiments which involved turning by hand the wheel of a cycle ergometer having a four kilo break. The mode of procedure was to work for ten minutes and rest for five minutes alternately for the space of an hour. During each five minutes of rest, the pulse was counted. The counting began at exactly fifteen

seconds after the cessation of the exercise and was continued every other quarter-minute until eight counts were made. Thus four minutes elapsed and the remaining minute of rest was devoted to reading the ergometer and in getting ready for the next ten minutes of work.

In the course of these experiments an acute naso-pharyngeal infection occurred and two tests were performed while the subject was "under the weather" (May 17 and 19). On comparing the effect of the muscular exertion upon the heart rate, we find *a*, that the heart rate is much higher during the infection than before while the work done is on the average less; *b*, that the heart rate is no less during the infection than afterward while the work done is much less. The rise in the heart rate after the period of infection as compared with that before infection is the result of practice which permits a great increase

TABLE 10
Effect of acute infection on the response of the heart rate to exercise

DATE	PULSE RATE					NUMBER OF REVOLUTIONS
	Before exercise	After each heat				
		1st	2d	3d	4th	
May 5, 1919.....	55	21-15	24-16	27-17	27-19	5610
May 17, 1919.....	56	29-19	28-20	30-20	30-19	5157
May 19, 1919.....	53	30-19	34-20	32-21	32-22	5992
June 9, 1919.....	59	30-20	34-22	32-21	34-23	7098

Average
5574

in the number of revolutions accompanied by an increase in the heart rate without however any untoward effects. But the infection causes increase in the heart rate without permitting any corresponding increase in the amount of work done, and the exertion in this case distresses the subject to a considerable extent.

Table 10. In the *first* column is shown the date of the experiment; in the *second*, the pulse rate per minute before exercise; *third*, the pulse rate after the first ten minutes of work, the first figure representing the first reading, the second figure the last reading in the first four minutes following the first heat; *fourth*, *fifth* and *sixth* observations after the second, third and fourth heats respectively; in the *seventh*, the total number of revolutions in all four heats. May 5 and June 9 are before and after the infection respectively. May 17 and 19 are during the infection. *Note that during infection the reaction of the pulse rate to exercise is increased while the number of revolutions (amount of work done) is not increased.*

Exercise and distress. A few notes were made of the feeling of distress which occasionally occurred *during* exercise ('14-run). Here there seemed to be no discoverable connection between these symptoms and the extent of the disturbance of the pulse rate or blood pressure subsequently obtained (at the end of the run) nor between the symptoms and the return of the pulse rate toward normal. For example, on May 22 and April 17 following distress, the pulse rate was 120 and 100 respectively while no untoward symptoms occurred on May 1, 2 and 8 when the pulse rate at the end of the run was 150, 120 and 96 respectively.

Following exercise there may be a feeling of distress which consists of giddiness or nausea or both. This does not necessarily occur during the negative phase. It may occur some minutes after the exercise has ceased. It was of momentary duration in every case except after the first bicycle ride in 1914. In the latter case the sequence of events was as follows:

TIME	S.	D.	P.R.
5.08 p.m. cessation of exercise			
5.19	116	90	90
Began to feel faint			
5.20	118	90	
5.21	116	92	
Kneeling with head touching floor			
Feeling better, head still low			
5.25	118	90	52
Head raised, still kneeling			
5.26	118	88	88
5.27	116	88	80
5.28	116	88	126
Sitting on bicycle again			
5.30	115	88	
5.35	116	90	126
Subject lies down			
5.43	108	80	76 recumbent
5.48	106	80	82 recumbent
Subject changes clothes partly			
5.57	118	76	76 recumbent
Finished dressing			
6.05	124	80	74
Dinner with staff of medical school followed by discussion			
10.00	115	75	67 recumbent
10.00	118	80	84 standing

A satisfactory interpretation of this attack must await more extensive observation and the following explanation is little more than a conjecture. It appears to the writer as if the primary factors were cardiac. A sudden drop in the pulse rate (from 90 to 52) causes cerebral and systemic anemia, a powerful, peripheral constriction restores the blood pressure (reading B.P. 118-90, P.R. 52). Then the peripheral constriction all the time compensating the changes in pulse rate, the latter rises, runs beyond the mark, falls again, rises again, and finally becomes tranquil. It is, of course, possible to conceive that the vascular change (constriction) is primary and is compensated by the changes in heart rate. But such a supposition seems unwarranted since it implies that the cerebral vessels share in the general constriction to a degree that renders the brain anemic, an exploit on the part of cerebral vasomotors which at the present time seems incredible.

Lastly it might be urged that perhaps the factor of peripheral resistance remains constant and that the factor which varies inversely with the heart rate (thus keeping the pressure constant) is the force (output) of the heart beat. But the writer is still addicted to the belief that such variations in systolic output are indicated by change in the pulse pressure and, since this does not occur, he is loath to entertain this explanation.

During the vicissitudes of the experiment Professor Eyster made the determinations for which I am indebted.

In 1916, distress was sometimes observed after cycle rides. On one occasion, April 14, fleeting faintness was felt and on the other, May 3, the symptom was an equally transitory nausea. On neither occasion did these symptoms last longer than the time required for a single pair of blood pressure readings. The faintness was not associated with any decrease in pulse pressure though the nausea may have been (fig. 10). Unfortunately, the pulse rate was not determined in these particular experiments. The symptoms on these two occasions differ from those in 1914, not only in being less severe but also in their time relations to the cessation of the exercise. Those of '16-cy-ten were within five minutes of the cessation of exercise (cycle) while that in '14-run was fifteen minutes after cessation of the exercise (cycle test).

SUMMARY OF RESULTS

The following summary is submitted without further discussion. Credit to previous investigators together with comment and criticism is reserved for a separate communication.

I. The effect of training upon the resting pulse rate, blood pressures and their derivatives was as follows:

a. The pulse rate was slowed especially the noon and afternoon pulses. This altered slightly the form of the diurnal pulse curve. The extent of the diurnal variation was increased.

b. The diurnal variations of the systolic pressure were increased.

c. The diastolic pressure approached the daily mean while its diurnal variations were much decreased.

d. The pulse pressure was usually increased and its diurnal variations were somewhat decreased.

e. The forms of the daily curves of blood pressures were not obviously altered.

f. The product of the pulse rate times the pulse pressure was usually increased but the character of its daily variations was unchanged.

II. The effect of training or of practice or of both upon the cardiovascular reactions to exercise was as follows:

g. When the trained or practiced individual engaged in physical exercise he naturally accomplished more work with less apparent exertion and less subjective distress. This was in spite of the fact that the systolic pressure rose higher, the pulse pressure increased enormously and with it sometimes the product $P.R. \times P.P.$

h. The diastolic pressure sometimes returned earlier to normal, i.e., while the exercise was still in progress.

i. The pulse rate however was sometimes less affected than in the untrained subject and probably reached normal before that of the latter.

III. The following interesting, miscellaneous observations were also made:

j. An acute infection (naso-pharyngitis) caused an increase in the pulse rate but no change in the blood pressures. In the trained subject the change in pulse rate was much less pronounced.

k. During acute infection (naso-pharyngitis) exercise caused a greater increase in pulse rate than with the normal subject and the amount of work accomplished was less.

l. The feeling of distress which occurred during exercise showed no relation to the heart rate and blood pressure determined at the cessation of the exercise. When distress followed exercise it had no relation to the blood pressure present at the time but the heart rate was found to be greatly decreased.

As already stated in the introduction (q.v.), these conclusions are subject to certain reservations.

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APPENDIX. ROUTINE OBSERVATIONS

TABLE A

14-run

DATE	MORNING		NOON		AFTERNOON		EVENING		REMARKS
	D. T.	P.R.	D. T.	P.R.	D. T.	P.R.	D. T.	P.R.	
April 1.....									Cycle test
April 2.....			116-88	50	120-98	59			
April 3.....			120-104	55	128-100	61			
April 4.....			124-90	67	122-92	62			
April 5.....			122-92	52					8 miles, walk and run
April 6.....									8 miles, walk and run
April 7.....									8 miles, walk and run
April 8.....									3 miles, walk and run
April 9.....			130-98	58					8 miles, walk and run
April 10.....									Gymnastics
April 11.....									12-mile walk
April 12.....	118-86				126-92	82			22-mile walk
April 13.....			116-82	50					Gymnastics
April 14.....		54	124-90	56	114-90	64			
April 15.....		54							3 miles, walk and run
April 16.....			120-86	64	120-82	60			
April 17.....					128-90	58			3 miles, walk and run
April 18.....									3 miles, walk and run
April 19.....	*	*	*	*	*	*	*	*	Coryza
April 22.....									3-mile run
April 23.....									
April 24.....		54							
April 25.....			122-88	56					
April 26.....									
April 27.....	*	*	*	*	*	*	*	*	3-mile run
April 30.....									3-mile run
May 1.....									3-mile run
May 2.....							128-88	56	3-mile run
May 3.....	111-85	54					96-74	59	13-mile walk
May 4.....	112-81	52							
May 5.....		53							
May 6.....					109-77	53	110-77	58	3-mile run
May 7.....	115-80	47			126-83	55	115-81	63	3-mile run
May 8.....	110-76	55			113-78	55			3-mile run
May 9.....			120-94	50	120-94	52			
May 10.....			114-87	51					
	*	*	*	*	*	*	*	*	

TABLE A—*Concluded*

DATE	MORNING		NOON		AFTERNOON		EVENING		REMARKS
	S. D.	P.R.	S. D.	P.R.	S. D.	P.R.	S. D.	P.R.	
May 13.....					113-83	59	105-75	63	3-mile run
May 14.....	107-85	58			120-87	63	108-85	64	3-mile run
May 15.....		55							
May 22.....					114-84	53	105-84	70	3-mile run
May 23.....	100-81	50	114-88	53	115-86	57	130-90	66	3-mile run
May 24.....	109-89	57	112-83	53	110-83	54	122-84	54	
May 25.....	106-81	48	112-91	52			119-90	68	
May 26.....	116-83	55	119-89	61	120-91	62	108-79	73	3-mile run
May 27.....	101-81	53			121-87	64	103-83	71	3-mile run
May 28.....	101-78	52	122-92	54	123-94	57	115-89	54	
May 29.....	108-89	49			117-90	52	119-95	55	Cycle test
May 30.....	106-82	50	117-85	48				57	
May 31.....		47		56		53		51	
June 1.....		54		51		53		58	
June 2.....		49		49		53			

TABLE B
15-gm.

DATE	MORNING		NOON		AFTERNOON		EVENING	
	S.-D.	P.R.	S.-D.	P.R.	S.-D.	P.R.	S.-D.	P.R.
March 5.....			112-88	64	118-84	60	111-85	59
March 6.....	109-82	57	107-82	58				
March 7.....			109-78	63			118-80	67
March 8.....	103-90	54	110-81	60	114-85	60	113-88	59
March 9.....	113-88	56	111-91	61			110-79	63
March 10.....	114-90	52			113-89	62		
March 11.....	114-86	54	126-85	61	118-91	58	118-86	62
March 12.....	112-85	58	110-89	60				
March 13*.....	109-77	69	114-91	55			114-78	60
March 14*.....	105-76	70	112-77	59			114-78	60
March 15*.....	108-77	72	108-79	61	120-90	63	117-86	64
March 16*.....	114-78	71					113-87	59
March 17*.....	108-75	69	117-86	69	113-80	64	116-86	60
March 18*.....	110-76	70					108-80	58
	*	*	*	*	*	*	*	*
March 21*.....	105-70	75					114-76	70
March 22*.....	113-76	74	116-88	62	116-87	63	117-81	66
March 23*.....	109-76	67			119-86	58		
March 24*.....		68	115-89	53				
March 25*.....	111-76	60					122-85	65
March 26*.....	116-84	66	116-92	60				
March 27*.....	111-77	72	115-88	65			115-84	72
March 28.....	115-78	57	112-86	57			123-81	61
March 29*.....	115-84	68	119-89	58			118-80	61
March 30*.....	109-79		114-87	56			125-79	70
March 31*.....	112-74	70			112-85	56	129-85	
April 1.....	111-77	53	117-85	53	118-85	56	120-86	55
April 2*.....	118-78	65	124-86	63	121-85	60		
April 3*.....	111-79	69			118-87	62		
April 4.....	117-84	51					117-75	67
April 5*.....	104-68	74			114-86	70	120-83	63
April 6*.....	111-75	65	113-82	60	118-89	56	120-95	62
April 7.....	113-82	53			114-87	55		
April 8*.....	111-75	67	107-83	56	115-87	60	121-82	60
April 9*.....	107-73	64	114-88	55	115-85	59	108-75	60
April 10†.....	104-68	62	119-93	51	117-85	63		54
April 11.....								
April 12.....	107-72	69	130-92	57			109-79	63
April 13*.....	105-77	73						
April 14.....		50	121-95		120-89		116-79	58
April 15.....	110-76	52	121-95	50	127-95	65	115-78	59
April 16.....	112-81	55						
April 17.....	110-80	55	122-88					
April 18.....		56						
April 19.....			124-91	60	126-93	62		

* Gymnastics on rising before making observations of pressure and pulse.

† Gymnastics in afternoon before observations.

TABLE C
'16-cy-len

DATE	MORNING		NOON		AFTERNOON		EVENING		REMARKS
	S-D.	P.R.	S-D.	P.R.	S-D.	P.R.	S-D.	P.R.	
March 30.....		55				62			
March 31.....		55							
April 1.....	101-67	55	118-75	66					
April 2.....	101-73	58			118-82	56	120-81	65	
April 3.....		63		72	126-83	85	118-73	86	
April 4.....	106-72	70	108-80	65	120-84	64	104-70	73	
April 5.....	109-72	57	113-86	65	117-86	57	107-79	63	
April 6.....	98-71	58	119-86	58	119-90	61	103-72	62	
April 7.....	99-73	59			115-78	59			
April 8.....	103-76	57	119-90	59			124-85	62	
April 9.....	103-73	61			106-78	66	120-90	66	Walk
April 10.....	100-76	61	110-81	57	118-89		115-83	62	
April 11.....	109-81	56	111-84	58	118-83	56	116-80	56	
April 12.....	100-72	57	110-80	56			114-79	79	Walk
April 13.....	101-79	57	114-84	55	114-84	55	121-88	58	
April 14.....	106-85	60	112-82	59	116-79	66	107-76	66	Cycle ride
April 15.....	100-77	56	116-90	60	111-87	54	112-79	65	Walk
April 16.....	97-71	54	109-79	56	116-78	65	98-68	70	Cycle ride
April 17.....	101-74	50	120-91	58	119-85	64	115-76	60	
April 18.....	103-76	56	121-91	56	115-79	60	107-78	63	Cycle ride
April 19.....	99-68	54	116-87	66	117-85	64	102-75	65	
April 20.....	96-64	56	106-78	66	111-82	60	112-76	70	
April 21.....	102-74	55			116-81	62	108-73	68	Cycle ride
April 22.....	105-70	53	114-80	64			116-81	65	
April 23.....	106-81	56	112-83	54			111-81	68	6-mile walk
April 24.....	100-77	56			110-80	72			
April 25.....		55					116-78	65	
April 26.....	107-77	59							
April 27.....	112-78	52			115-84	64	114-80	68	Cycle ride
April 28.....	102-72	54	109-81	56	116-88	59	100-70	62	
April 29.....	106-84	53	112-85	58	111-84	56			Cycle ride
April 30.....	107-83	53	106-80	59	113-80	58	100-79	56	
May 1.....	100-79	56							
May 2.....	102-76	63	112-86	62	112-82	62	116-81	64	
May 3.....	106-77	58	115-83	62	123-91	66	109-80	69	Cycle ride
May 4.....	105-78	57		56			119-84	58	
May 5.....	104-80	57	115-90				113-84	74	Tennis, walk
May 6.....	101-78	60	116-84	61	111-82	61	126-85	64	
May 7.....	108-78	57	109-81	55	111-77	68	110-80	72	Cycle ride
May 8.....	104-81	54	111-84	59	113-81	61	112-80	61	

TABLE C—Concluded

DATE	MORNING		NOON		AFTERNOON		EVENING		REMARKS
	D. S.	P.R.	D. S.	P.R.	D. S.	P.R.	D. S.	P.R.	
May 9.....	103-86	55	116-86	59					Tennis
May 10.....	105-83	58	113-84	56	115-82	58			
May 11.....	107-77	56	108-84	53					Tennis
May 12.....	107-76	54	115-86	57					
May 13.....	102-76	56	112-89	55			114-83	59	
May 14.....	107-79	53		64			113-80	64	
May 15.....	100-77	58	108-80	62			109-85	69	Tennis
May 16.....	108-78	55	112-84	53			107-82	69	Tennis
May 17.....	106-78	55	119-87	55	111-84	62	111-81	62	
May 18.....	108-80	57	109-81	56			115-79	64	Tennis
May 19.....	104-71	54	111-84	57	116-83	60	110-80	64	
May 20.....	113-77	59	113-83	60	114-85	59	116-84	61	
May 21.....	112-79	54					122-81	64	
May 22.....	110-78	55	115-82	52	117-84	62	104-73	72	Tennis
May 23.....	110-78	61	110-83				107-78	73	Tennis
May 24.....	108-77	59	110-77	52	121-84	60			
May 25.....			114-85	56			107-80	58	Tennis
May 26.....	106-81	55	120-84	60			112-79	58	Tennis
May 27.....	105-72	53	112-80	51			110-77	64	Tennis
May 28.....	102-71	56	113-81	47		60	115-82	60	
May 29.....	112-82	48	109-83	47	117-86	49	115-77	56	
May 30.....	106-79	52	112-83	50			111-81	58	Tennis
May 31.....	105-76	53	114-84	50	109-82	53	116-76	56	
June 1.....		53	114-82	50					Tennis
June 2.....	105-79	58	113-81	58					Tennis
June 3.....	98-77	54	112-79	48	115-77	59	115-77	59	Tennis
June 4.....	105-78	49	107-81	48			116-80	53	
June 5.....	108-80	50	106-77	53					
June 6.....	108-80	52	115-83	48	115-80	53			Cycle ride
June 7.....	112-74	52	112-83	53	116-79	56			Cycle ride
June 8.....	110-80	54	118-88	56	119-86	61	112-78	69	
June 9.....	115-79	63	118-81	59	116-83	61	118-77	63	
June 10.....	106-77	55	115-81	54			115-78	66	
June 11.....	99-70	59	110-80	53	117-81	56	119-76	59	
June 12.....	101-76	55	120-83	55					Tennis
June 13.....	107-77	59	112-79	59			113-80	70	Tennis
June 14.....	110-77	62	112-79	58					Tennis
June 15.....	107-76	58	115-85	57			108-78	59	
June 16.....	102-79	55	112-80	48			116-80	59	
June 17.....	104-78	54	118-83	50					